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THE WATER METABOLISM OF NEWBORN INFANTS AND ANIMALS*

BY

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(Received for Publication October 3, 1950)

Clinical experience leaves no doubt that the water metabolism of infants differs from that of normal adults. This difference emerges not only from the well known facts that an apparently small decrease of fluid intake or increase of the fluid loss may produce clinical symptoms of dehydration, but it is also evident from the ease with which oedema may be produced by ' therapeutical ' administration of fluids to newborn children.

In practice dehydration in infants mainly seems to occur in two conditions. First, where a normal intake of food is not balanced by a sufficient intake of water (Rietschel, 1934; Finkelstein, 1938). Secondly, when diarrhoea and vomiting lead to excessive losses of fluid and certain electrolytes.

Dehydration undoubtedly remains the chief cause of the continued high fatality rate in cases of infantile diarrhoea and vomiting. Its prevention or early correction constitutes the most important factor influencing recovery. However, the therapeutic problem in cases of dehydration is clearly not a simple one: the amount and composition of the fluid to be given and the route of administration require careful consideration and if, as may be necessary, intravenous application has to be chosen, the rate of infusion will also need to be watched carefully. Decisions as to therapeutic measures covering these factors have frequently still to be made on empirical grounds. It is therefore not surprising that instances of gross oedema are observed (Arnott and Young, 1942; Alexander, 1948). Death in infants after intravenous administration of fluids has also been ascribed to cardiac failure due to overloading of the circulation (Alexander, 1948).

Water depletion and salt depletion will have to be kept apart as in adults but it is clear that more knowledge of the water metabolism of infants is required. The analysis of the effects of dehydration and rehydration in adults forms the necessary basis for such studies, but it would clearly be a serious mistake to apply the results of work on adults unreservedly to newborn infants. It is equally evident that investigators concerned with a comparison between the water metabolism of infants and of adults will have to consider a variety of factors which are either known, or which may be suspected to operate differently in the newborn. These differing factors may be grouped as follows: (*a*) differences in the internal environment of the newborn, i.e. differences in the solute composition and the relative volumes of the extra and intracellular fluid phases, (*b*) differences in renal development and function, (*c*) differences in the functional state of integrative structures, namely of the endocrine glands and the hypothalamic structures which regulate or influence the metabolism of water and the electrolytes. Some of these factors and their interplay can and have been studied in infants. However, the limitations inherent in clinical investigations necessitate in many instances recourse to animal experiments.

A certain amount of preliminary but very valuable and interesting work on animals was done by continental investigators, notably by Kerpel-Fronius (1932). This work has been much expanded during recent years, thanks mainly to the stimulus given by the development of the renal clearance techniques by H. W. Smith and the clinical investigations of McCance and his co-workers. It is therefore proposed to discuss some of the recent results obtained in newborn mammals and to compare the findings so far as possible with those in newborn infants. It may be well to emphasize in this connexion that results obtained in newborn animals should not be regarded as complementary to findings in newborn infants, even if the conditions under which they were obtained are reasonably comparable. This necessity arises less from species differences in the regulatory mechanisms and effector systems concerned than from species differences in the maturity at birth. Newborn rats, for example, are markedly less mature at birth than newborn children; newborn guinea-pigs, on the other hand, are, according to most criteria, considerably further developed than either. These differences in maturity

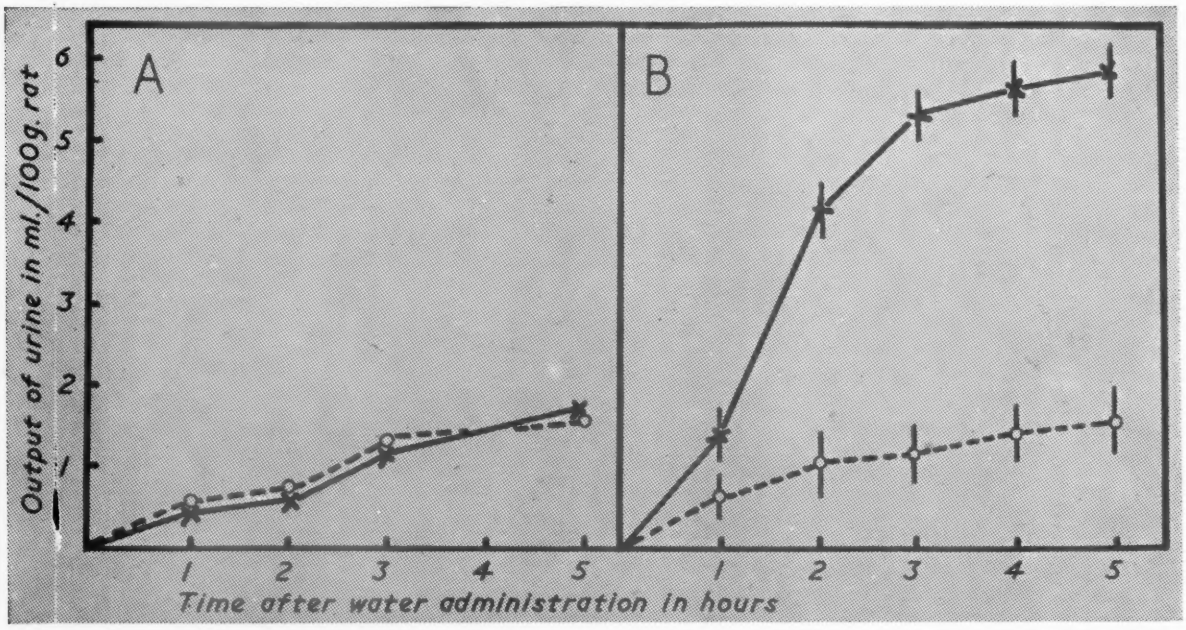
* A lecture given in the Department of Paediatrics, Harvard University, during the tenure of a visiting professorship at New York University Medical School.

have perhaps certain advantages for the experimental worker. When we decided some years ago to study certain aspects of the water metabolism in newborn mammals, newborn rats were deliberately chosen because it was hoped that any deviations from the adult would be more easily recognizable in such immature animals. It is interesting to note that quite independently newborns of the same species were selected by the Cambridge workers (McCance and Wilkinson, 1947).

The primary function of the mechanisms which regulate the water metabolism of animals consist in keeping the body water constant within narrow bounds. This implies that the organism is able to eliminate extra water in a comparatively short time and, on the other hand, that the internal environment remains intact even though water intake is intermittent and renal and extrarenal loss continuous.

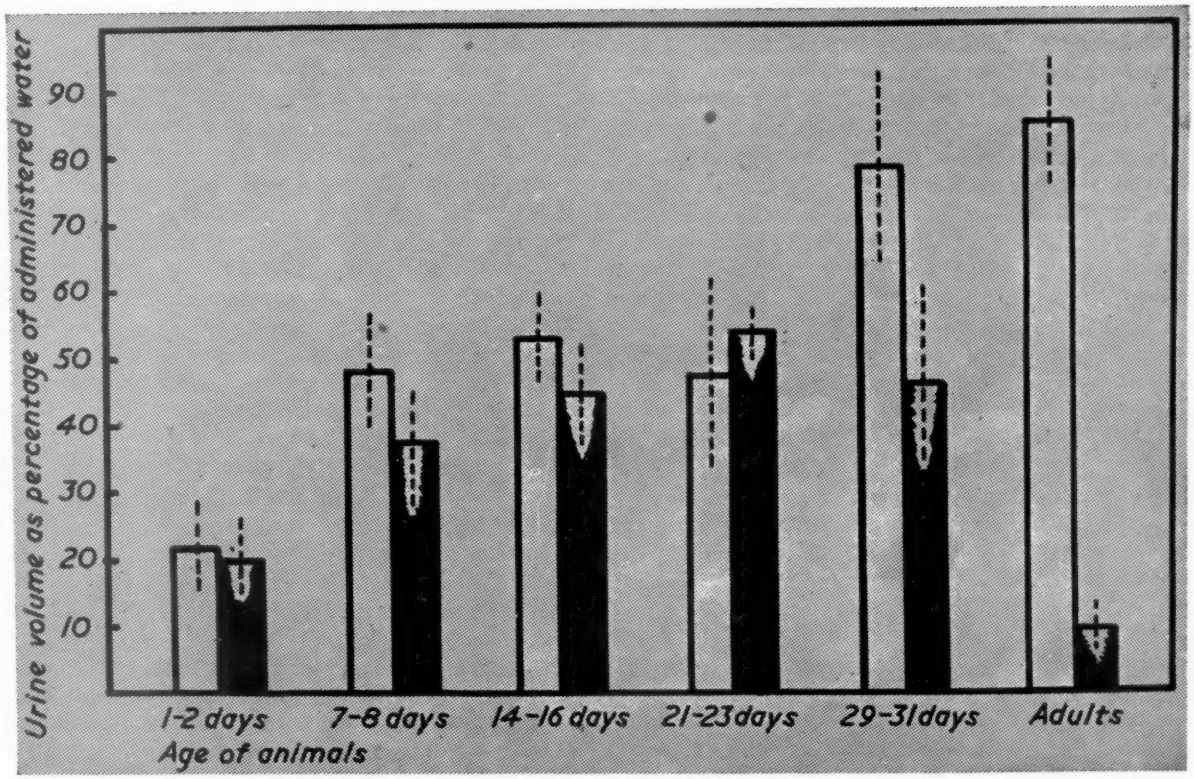
It was therefore decided to investigate first how newborn rats react to an alimentary water load which is easily and quickly disposed of by adult animals (Heller and Smirk, 1932a), and secondly to study the response of the newborn rats to degrees of dehydration which, as regards their internal environment, are well compensated by adult rats by means of their highly developed osmoregulatory mechanisms.

The first problem centres on the question whether newborn animals exhibit an adult type of water diuresis. It was found (Heller, 1947a) that the response of newborn rats differs markedly from that of adults. When 4·5 g. water/100 g. were placed in the stomach of rats aged 24 to 48 hours and the urinary output was measured for the following 5 hours, no evidence for an increase of urinary output could be obtained (Fig. 1). The method of urine collection used in these experiments was not sufficiently accurate to be certain that a response to water administration was entirely absent; micturition in newborn rats is not spontaneous and urine output had to be determined by averaging the weight of urine contained in the bladder of series of animals killed at given times after water administration. However, it is sufficiently clear that any increases of urine volume must have been very small at best. It should be mentioned here that the newborn rats in which these results were obtained were kept at an environmental temperature of approximately 31° C. This temperature was chosen because full capacity for thermoregulation is only acquired by rats during the fourth week of extrauterine life (Brody, 1943). Newborn rats derive much of their warmth from the mother, i.e. from the contact with a surface of about 31° C. (Herrington, 1940). It did, therefore, seem to be



A. X——X = mean urinary output of *newborn* rats after the intragastric injection of 4·5 ml. water/100 g. rat. O — — — O = controls.
B. X——X = mean urinary output of *adult* rats which received 4·5 ml. water/100 g. by mouth. O — — — O = controls.
The vertical lines indicate the standard error.

FIG. 1.—Comparison between the urinary output of newborn and of adult rats after administration of water by the stomach (Heller, 1947a).



□ = mean urine volume of urine 145 minutes after the administration of 4·5 ml. water/100 g. by stomach tube.
■ = mean urine output of litter mates 145 minutes after the same amount of water and the injection of 10 mU vaso-pressin/100 g. rat.
The broken lines indicate twice the standard error of the mean.

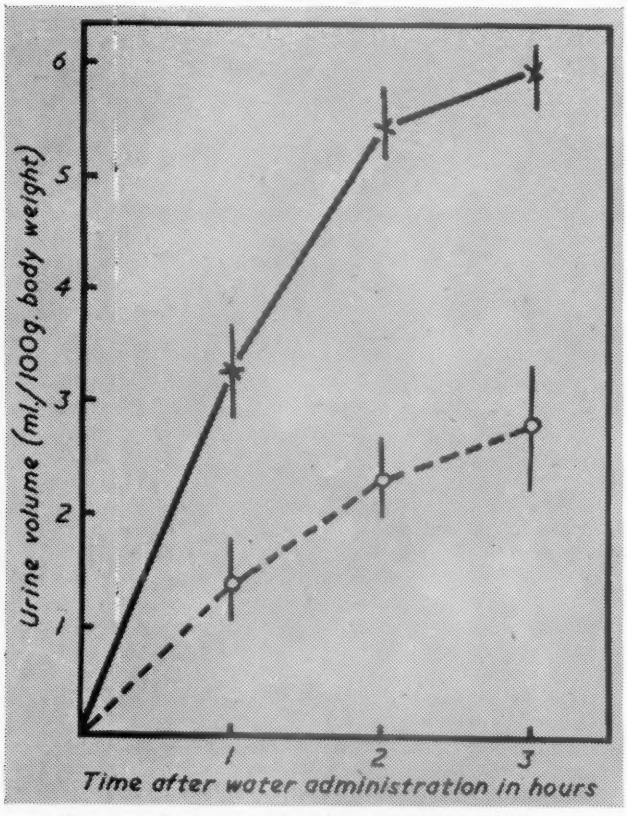
FIG. 2.—Development of the response to water administration and to the injection of posterior pituitary anti-diuretic hormone in rats. It will be noted that only in the rats aged 4 weeks the urine volume approximated to that of the adult animals, a small but significant anti-diuretic response to the posterior pituitary hormone was found in rats of the same age (Heller, unpublished experiments).

more advisable to conduct ' physiological ' experiments at about 31° C. than at room temperature which would lead to considerable undercooling. However, it has been shown by Heller and Smirk (1932b) that keeping adult rats at raised environmental temperatures leads to an inhibition of water diuresis which is not due to the increased extrarenal water loss. Was the failure to obtain water diuresis in newborn rats caused by an unduly high temperature ? Experiments done on newborn rats kept at lower air temperatures excluded this possibility. On the contrary, they revealed the remarkable fact that the urinary output increased markedly with a rise of environmental temperature: newborn rats at 20/21° C. excreted a mean of 0·52 ml./100 g. in four hours; newborn rats at 30/31° C. excreted 1·23 ml./100 g. in four hours. Similar findings have been made in frogs (Krause, 1928), but it was surprising to find this feature in a mammalian species. It can be concluded from these results that the virtual absence of water diuresis in our series of newborn rats was not due to heat inhibition. McCance and Wilkinson (1947) found similarly that newborn rats were unable to excrete administered water, that the minute volume of urine rose slightly in animals aged four days and that it increased considerably in rats aged 12 days. It will be seen from Fig. 2, which compares the response of adults with that of rats aged from 1 to 28 days, that adult values are reached during the fourth week after birth.

How do rats compare in this respect with the newborn of other mammalian species ? The results of Adolph (1943) on puppies indicate that an incompletely developed ability to reduce an excess water load by the renal route is not restricted to newborn rats, and an investigation of the renal function of newborn guinea-pigs which has recently been completed (Dicker and Heller, 1951) shows that the same applies to this species. Guinea-pigs, as already mentioned, are by all available criteria much more mature at birth than rats. (The incisors of rats, for instance, erupt only after eight to 10 days of extra-uterine life, whereas in the guinea-pig they

are present at birth.) It is in keeping with these developmental differences that water diuresis in newborn guinea-pigs is already quite pronounced though administered water is still excreted at a considerably lower rate than by adults (Fig. 3). Judging from the scanty evidence available it would appear that infants show the adult response to water administration comparatively late: Aschenheim (1919) and Lasch (1923) found that infants aged up to 3 months of age excreted a dose of water given by mouth at a much slower rate than babies in the second half year of life. It is clear, however, that these results will have to be repeated in more closely defined age groups and with adequate adult controls.

Why is water diuresis less well developed in the newborn than in the adult? Many factors which are known to influence the course of a water diuresis have still to be investigated before this question can be answered. However, some indications of the different manner in which newborn mammals handle administered water were obtained from our comparison between adult and newborn rats. For instance, the rate of water absorption from the gastro-intestinal tract was measured and it was found that newborn rats absorbed water more slowly than adult animals of the same strain. This delay in the alimentary water absorption which may be due to adrenal cortical or anterior pituitary hypofunction (Clark, 1939; Gaunt, 1944; Joseph, Schweizer, Ulmer, and Gaunt, 1944) would by itself lead to some decrease in the rate of water excretion. However, it could be shown that this is only a minor factor which modified water diuresis in the newborn animals. Further investigation indicated that the newborn rats were unable to excrete 'extra water' at the adult rate even after absorption from the gastro-intestinal tract had been completed.



O — — — O = mean urine volume of *newborn* animals.
X——— X = mean urine volume of *adult* animals.
The vertical lines indicate the standard error.

FIG. 3.—Comparison between the urinary output of adult and of newborn guinea-pigs after the administration of 5 ml./water/100 g. body weight by mouth (Dicker and Heller, 1951).

Determinations of the rate of extrarenal water loss revealed that newborn rats kept at 20/21° C. (i.e. at room temperature) lost much less water extrarenally than adults at the same temperature. Newborn rats kept at 30/31° C., lost water extrarenally at about the same rate as adult animals at 20/21° C. These results show that the extrarenal loss during the five hours after water administration cannot account for the virtual absence of water diuresis, and since alimentary water absorption in the newborn rats was shown to be completed in about three hours and the urine volume hardly increased during this time, it follows that any of the administered water residual after this period was lodged in the extra-alimentary tissues. In a series of newborn rats kept at 30/31° C. for instance, this residual or tissue water load after three hours amounted to about 70% of the dose administered and to about 60% five hours after the water had been given. In other words, a dose of water which, owing to the quick alimentary absorption and renal excretion, increases the tissue water load of adult rats slightly and for a short period only (Heller and Smirk, 1932a) led to a state of 'oedema' in normal newborn rats. It remains to be seen whether the residual water is uniformly distributed in the tissues of the newborn rats or whether the oedema is localized as after water administration to hypoproteinaemic rats with an already expanded extracellular fluid space whose water metabolism resembles in many ways that of the normal newborn animals (Dicker, 1950). These findings in rats may prove of some interest in connexion with the comparative frequency with which oedema after parenteral administration of fluid has been observed in newborn infants. A comparison between the response of adults and infants to the same relative

extra water load may show that the factors which operate in newborn rats contribute—though perhaps to a minor degree—to the occurrence of oedema in the newborn child.

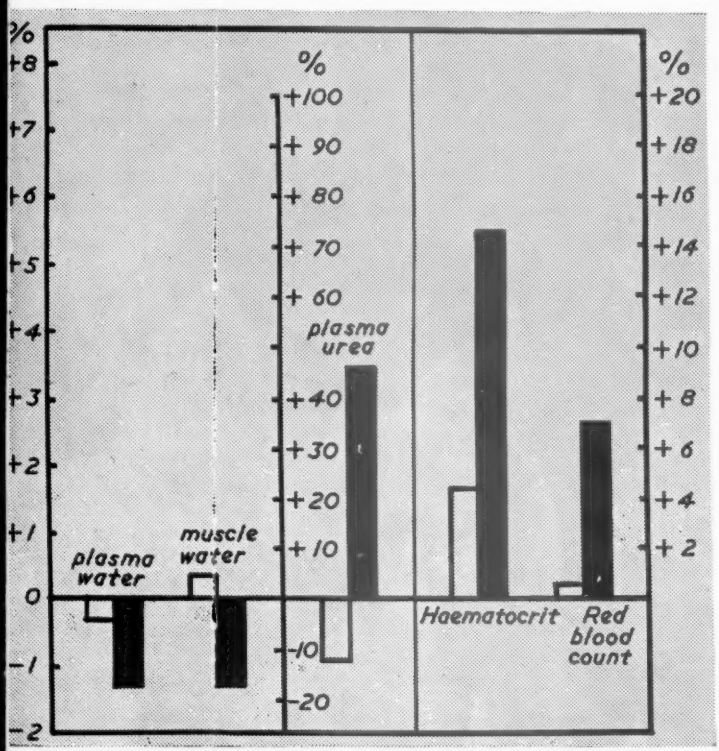
However, judging from a report of Gaisford and Schofield (1950) a distinction may have to be drawn between premature infants and those delivered at term. Premature infants, according to the experience of these authors, stand withdrawal of fluid for the first three or four days after birth comparatively well. This may be partly due to the well known fact that many premature babies show signs of oedema at birth. Gaisford and Schofield, for instance, observed oedema in 9% of their cases, and the incidence in Hallum's (1941) series was as high as 13·4% in contrast to 1·2% in children born at or near full term. It may be assumed from similar findings in cases of oedema of malnutrition (Dicker, 1948) that the occurrence of 'visible' oedema corresponds to a far larger number of cases in which the extracellular fluid space is abnormally increased even though the oedema is not clinically recognizable. A beneficial effect of fluid restriction in infants suffering from visible or occult oedema can thus be postulated when fluid and food are withdrawn for a short period; the measure would act as a stimulus for the excretion of extra body water. A similar effect has frequently been observed in this laboratory: animals suffering from an expansion of the extracellular fluid space due to protein deficiency frequently showed, when deprived of water and food, a paradoxical diuresis; in other words, they excreted oedema fluid (Dicker, Heller, and Hewer, 1946). Different effects may be expected when fluid losses occur in full term infants and animals. The size of their fluid compartments is probably optimal and losses of body water are therefore likely to lead to abnormalities of the internal environment.

To compare the effects of dehydration in adult and newborn rats fluids and food were withdrawn from both series of animals for 24 hours, and the environmental temperature of the newborns was so adjusted that their extrarenal water loss approximated to that of the adult animals. The results of the experiments (Heller, 1949) showed that adult rats responded to the withdrawal of water (and food) for 24 hours in much the same manner as human adults (Nadal, Pedersen, and Maddock, 1941) and adult dogs (Elkinton and Taffel, 1942; Elkinton and Winkler, 1944). The urines excreted at the end of the period of water deprivation were—as one could expect—highly concentrated. The mean urine volume fell from 10·6 to 1·5 ml./100 g. in 24 hours. The mean extrarenal water loss was high (5·5±0·20 g./100 g. in 24 hours) which is in accordance with the relatively large body surface of the small species investigated. The obligatory expenditure of water (made up of the amounts lost from skin, lungs, and the alimentary tract and the volume needed for the adequate excretion of solutes in the urine) must clearly have made demands on the extracellular fluid of animals whose only source of fluid consisted in the metabolic water derived from body reserves. However, not only was the normal ionic composition of the plasma on the whole maintained, but the extracellular fluid volume and particularly the plasma volume were also well defended: no marked increase in plasma solids and little change in the haematocrit and the red cell counts were found after 24 hours of dehydration. In view of the magnitude of the total water loss, the avoidance of haemoconcentration can only have been achieved by a shift of intracellular water. An increase in the renal excretion of the intracellular electrolyte potassium was observed in the dehydrated adults, which is in agreement with this conclusion. The plasma potassium level of the dehydrated adults was not significantly raised. Similarly, a decrease of cell potassium without an increase in plasma potassium has recently been demonstrated by Elkinton, Winkler, and Danowski (1948) in adult dogs deprived of water.

It would then seem that in adult rats the renal functions involved in the balancing of fluid losses after 24 hours of dehydration consist in an adequate ability to clear surplus crystalloids from the plasma, and it seems likely that one of the mechanisms concerned in this is a relatively unimpaired rate of glomerular filtration: no significant rise of the plasma urea, such as would occur with a substantial decrease of glomerular filtration (Gamble, 1947), could be found in the adult animals. The other renal activity concerned in this 'defensive' process is the tubular function of concentrating the urine to hypertonic levels.

How do newborn rats deprived of fluid and food for 24 hours differ in their response from that of adult animals? It could first be shown that the concentration of the urine increased much less than in the adults. Estimations of the urine/plasma ratios of chloride, sodium, potassium, and urea agreed with this finding. More water per unit weight of urinary solids was therefore excreted by the newborn rats but the difference between the 24-hour urine volumes of the dehydrated newborns and adults proved to be smaller than expected. This suggests that, in newborn rats which have been deprived of fluid for a comparatively short time, the renal loss of water is decreased by some mechanism additional to tubular water reabsorption. It seems justifiable to suspect that this mechanism is a decrease

in the rate of glomerular filtration. First, the results of Dicker obtained in this laboratory suggest a correlation between urine volume and glomerular filtration rate in the infant rat; and secondly, the occurrence of a substantial fall in the volume of glomerular filtrate is a well known response in adult men and in dogs suffering from advanced dehydration, i.e. from a degree of water loss which produces haemoconcentration and a decrease of the blood volume (Smith, 1937; Kenney, 1949.) A defence mechanism which operates in all age groups would thus also be invoked in the newborn animals but after much shorter periods of fluid deprivation than in adults. Significant reduction of the rate of glomerular filtration in infant rats during the first 24 hours of fluid withdrawal is also suggested by the observation that, unlike in the adult animals in which potassium excretion was increased, the renal elimination of potassium fell to about half of the normal value and that, again in contrast to the adult controls, their plasma urea had markedly increased (Fig. 4) at a stage when that of normal infant rats begins to fall. A considerable rise of plasma osmotic pressure in the dehydrated newborns seems therefore likely, and the highly interesting experiments of McCance and Wilkinson (1947) have shown how badly fitted the kidney of newborn rats is to cope with abnormal osmotic load. These authors administered hypertonic sodium chloride solutions to adult and to newborn rats, but while the adult animals responded by reducing the osmotic pressure of their urine and by producing a large diuresis which enabled them to excrete 27% of the electrolytes in five hours, newborn rats given a similar dose responded by raising the urinary osmotic pressure but failed to produce a diuresis and excreted only 6% of the test dose in the same time. Hypertonic solutions of urea produced effects similar to those of sodium chloride in both the adult and the newborn rats.



The columns show percentual deviations from mean values obtained in normally hydrated controls.

□ = adult animals. ■ = newborn animals (redrawn from Heller, 1949).

FIG. 4.—Effects of withdrawing fluid and food for 24 hours from adult and newborn rats.

To sum up: newborn rats deprived of water for 24 hours were unable to economize body water by concentrating the urine to the same extent as adults. Some economy in water excretion was probably achieved by a decrease in the glomerular filtration rate but at the price of the retention of certain crystalloids. In contrast to the adults, their plasma and tissue solids were found to be significantly increased as were the haematocrit values and the red cell count (Fig. 4). These findings show, therefore, that the defence of newborn rats against dehydration was less effective than that of adult animals under comparable conditions of stress, i.e. the internal environment of the adults deviated less from the normal.

The response of newborn infants to fluid restriction shows certain similarities to that of newborn animals. Accumulation of electrolytes and urea in the plasma of dehydrated infants has been described by numerous authors (Kerpel-Fronius, 1932, 1940; Young, Hallum, and McCance, 1941; Rapoport, 1947; Smith, Yudkin, Young, Minkovski, and Cushman, 1949) but it is not easy to deduce from these investigations to what degree the response of infants differs from that of adults under quantitatively comparable conditions of this kind of stress. It appears from the carefully controlled experiments of Dean and McCance (1949) that newborn infants are less capable of disposing of excessive osmotic loads than are adults. In parallel to the experiments on newborn rats, which have already been described, Dean and McCance administered hypertonic sodium chloride or urea solutions to adults and newborns after 15 hours of fluid deprivation. The adult subjects responded with a rapid and extensive diuresis accompanied by a fall in the urinary osmotic pressure, but the urine flow in the newborn infants increased only slowly and to a very moderate degree, and a rise rather than a fall in the osmotic pressure of the urine was found. Certain well

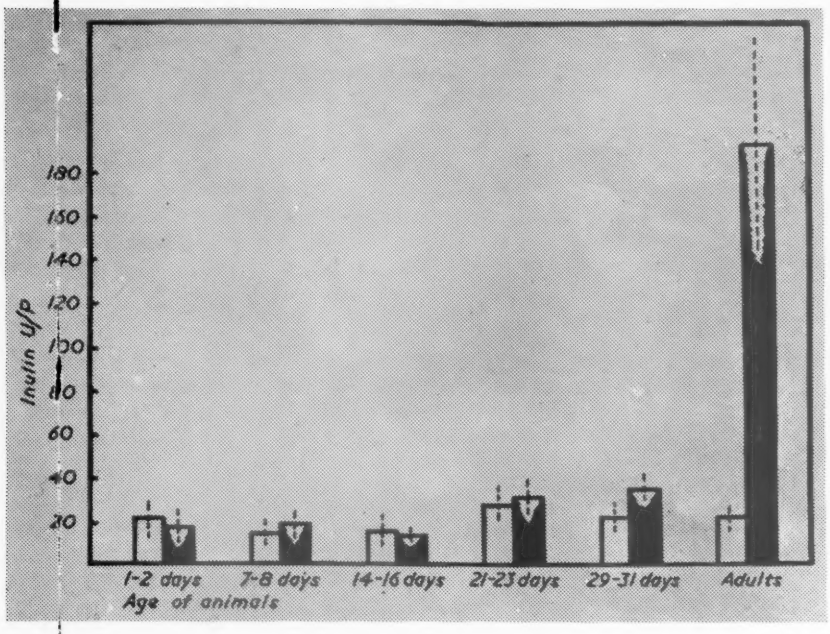
established features of the kidney function of newborn infants suggest an explanation for the differences observed. It is generally agreed (Young and McCance, 1942; Dean and McCance, 1947; West, Smith, and Chasis, 1948; Barnett, Hare, McNamara and Hare, 1948; Rubin, Bruck, and Rapoport, 1949) that the rate of glomerular filtration is much lower in infants than in adults, though there is no unanimity as to the closeness of the relationship between the glomerular filtration rate and the minute volume of urine (Barnett, Perley, and McGinnis, 1942; Young and McCance, 1942; Barnett *et al.*, 1948; Dean and McCance, 1949; Tudvad and Vesterdal, 1949). The clearances of urea, chloride, sodium, and potassium are low. It is justifiable to assume that the low glomerular filtration rate accounts partly for the low clearances but there is as yet insufficient evidence available to state to what extent renal tubular factors are participating. That is to say, it is not known whether the tubules reabsorb more of the filtered crystalloids in infancy than they do in adult life. This appears to happen in the case of chloride in newborn infants (Dean and McCance, 1949), and is likely to apply to other crystalloids, not necessarily because of a difference in the reabsorbing capacity of the tubular epithelium but perhaps, as suggested by Pitts and Duggan (1950), from their results on sodium absorption in adult men and dogs, because a lowered rate of glomerular filtration increases tubular reabsorption.

Although sodium and chloride seem to be excreted in a similar manner, recent work suggests that potassium excretion requires special consideration. Potassium is normally filtered and partially reabsorbed (Winkler and Smith, 1942; Dicker, 1948) but in certain conditions, for instance in chronic glomerulo-nephritis in men, some potassium is apparently secreted by the tubules (Berliner and Kennedy, 1948; Mudge, Foulks, and Gilman, 1948; Leaf and Camara, 1949). Another condition which provokes potassium secretion, at least in rats is, according to Dicker (1951), dehydration. This observation may explain a finding which had already been mentioned, namely the depression of the potassium excretion in dehydrated (and starving) infant rats which was in marked contrast to the rise of potassium elimination in adult controls. Tubular secretion would easily remove any potassium released by the breakdown of tissues in the adult animal while increased absorption due to low glomerular filtration in the dehydrated newborn could not be compensated because of immaturity of the secretory mechanism. The capacity for tubular secretion of *para*-amino hippurate and diodone has so far not been investigated in newborn rats, but there is general agreement (Dean and McCance, 1947; West *et al.*, 1948; Rubin *et al.*, 1948; Barnett *et al.*, 1948) that it is lower in newborn infants than in adults. It would also seem (Dean and McCance, 1947; Brod and Sirota 1948) that the secretory mechanism for creatinine, i.e. for an endogenous substance, is not fully developed in infants. A generalized immaturity of tubular secretory function in newborns is thus strongly suggested.

It will be remembered that another feature which distinguished the response of newborn rats from that of adult animals to dehydration consists in the apparent inability to concentrate their urine to the same degree as the adult. What is the concentrating ability of dehydrated newborn infants? A study of the specific gravity and osmotic pressure of urine samples obtained from normal newborn infants during the first days after birth shows immediately that their kidney is a more mature organ than that of newborn rats. The range of osmotic pressure values is very much wider; that is to say, in spite of the similar nature of their food, infants both dilute and concentrate their urine much better than newborn rats. In fact, measurements obtained during the first 48 hours, i.e. during the period of 'physiological hydropenia' show that slightly hypertonic urines can be elaborated by normal infants (Heller, 1944). Values of 450 m. osmol./l. and over were obtained and urines of still higher concentration can be prepared, when the dehydration of the newborns is intensified. Smith and his colleagues (1949) who investigated premature babies after periods of fluid (and food) deprivation lasting from 52 to 112 hours obtained values up to 624 m. osmol./l. and the findings of Barnett *et al.* (1948) point in the same direction. But can infants produce urines as concentrated as adults? The mean concentration of urines from normally hydrated healthy subjects in Heller's (1944) series was 900 m. osmol. and considerably higher figures (up to 1,300 m. osmol./l.) have been obtained when adult subjects underwent a short period of water deprivation.

Why does the kidney of newborn infants and animals appear to be unable to concentrate the urine to the same extent as adults? The question is clearly of considerable complexity but here only some endocrine aspects will be briefly discussed.

It is generally agreed that the posterior pituitary-renal mechanism constitutes the major determinant of the final urinary concentration in normal adults. The inability of the kidney of the newborn to concentrate suggests a possible inadequacy of this mechanism at birth. There can be little doubt that both in hydropenic infants and in dehydrated newborn animals the adequate physiological stimulus



□ = mean inulin U/P ratios 145 minutes after the administrations of 4·5 ml. water/100 g. by stomach tube.

■ = mean inulin U/P ratios 145 minutes after the same amount of water and the injection of 10 mU. vasopressin/100 g. rat. The broken lines indicate twice the standard error.

FIG. 5. Effect of posterior pituitary antidiuretic hormone on inulin urine/plasma ratios in rats. A small but significant response to the posterior pituitary extract will be noted in the rats aged 4 weeks. The renal response to the antidiuretic hormone at this age is, however, clearly much less developed than in the adult animals (Heller, unpublished experiments).

for an increased secretion of the posterior pituitary antidiuretic hormone (Verney, 1948), namely an increase of plasma osmotic pressure, is present. However, there is the possibility that the hypothalamic structures concerned with this regulatory mechanism are too immature to transmit it, or that the gland elaborates insufficient amounts of the antidiuretic hormone, or again that the kidney of the newborn is less sensitive to it than the adult organ. The second possibility, i.e. lack of antidiuretic hormone, may conceivably apply in rats since it has been shown (Heller, 1947b) that the pituitary gland of the newborn of this species contains only about one-tenth of the antidiuretic principle in the glands of adult animals. It is less likely to apply to newborn infants: a recently completed series of estimations of the antidiuretic hormone content of the posterior lobe of newborn infants (Heller and Zaimis, 1949) showed that these glands, though containing per mg. only about one-fifth of the activity of adult posterior pituitary tissue, contained all the same several hundred milliunits of the antidiuretic principle. There is evidence (Heller, unpublished experiments) on the other hand, that the renal tubules of newborn rats are less sensitive to the antidiuretic hormone than those of adults (Figs. 2 and 5) and the same appears to apply to newborn infants. It will be seen from Fig. 6, for instance, that after the intramuscular injection of a large dose of posterior pituitary extract the osmolar concentration of the urine of an infant increased to more than twice the initial value.

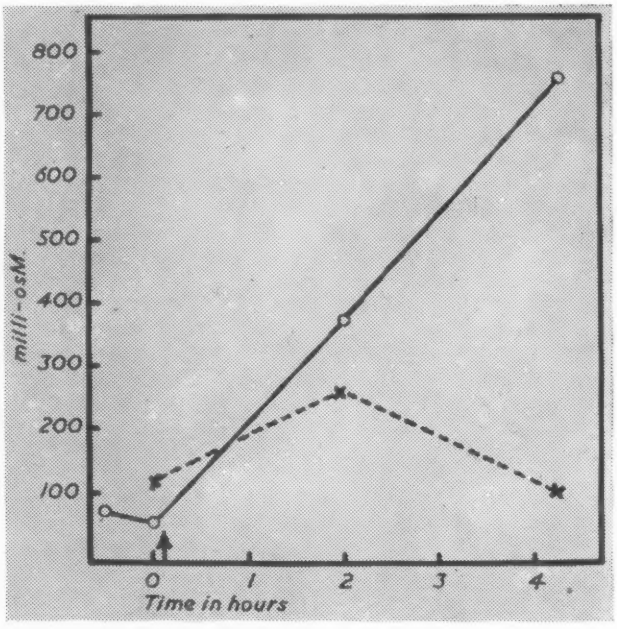


FIG. 6.—Comparison between the effect of equivalent doses of posterior pituitary extract on the urinary osmotic pressure (in terms of milli-osmolar equivalents) of an infant aged 5 days (X— — —X) and of an adult control (O———O). At the time marked by the arrow intramuscular injection of 0·25 U. of posterior pituitary extract per sq. m. body surface. Absolute doses = 0·05 U. and 0·5 U respectively. It will be noted that the initial osmolar concentration is much the same in both subjects (Heller, 1944).

However, the same dose given to an adult control caused not only much higher urinary concentrations but showed also a much longer duration of the antidiuretic effect. Barnett and his colleagues (1948) using a difference technique (determinations of inulin U/P ratios) found likewise a considerable response to large intravenous doses of vasopressin in premature infants. They concluded that their results 'indicated a good response of the tubules of the premature infant to antidiuretic hormone.' They failed, however, to control their findings by comparable experiments on adults. Unfortunately, therefore, their results cannot be used for a quantitative assessment of differences between the responses of the neonatal and adult kidney.

Low sensitivity to the posterior pituitary antidiuretic hormone found in newborn infants may have some bearing on a pathological condition of older children and adults which had been termed 'nephrogenic' or 'vasopressin-resistant' diabetes insipidus. Infants suffering from this 'disease' are popularly known as 'water babies'. Recently published cases (Forssman, 1945; Williams and Henry, 1947; Dancis, Birmingham, and Leslie, 1948) show that we are dealing with a congenital and usually a hereditary defect. It seems likely that the renal tubules in such individuals fail to reach normal maturity. The apparently complete absence of an antidiuretic response to large doses of 'pitressin' (Dancis *et al.*, 1948) suggests moreover that the developmental deviation occurs some time before birth as normal full-term infants show at least a partial response to the antidiuretic hormone (Heller, 1944). Whether the renal abnormality is an anatomical defect or a failure to develop the biochemical substrate for the distal tubular transfer mechanism of water or both is an open question. It seems preferable to restrict the term diabetes insipidus to cases where insufficient secretion of the posterior pituitary hormone has been demonstrated and to regard the condition just described a separate pathological entity.

Were we concerned with adults, a discussion of other endocrine influences on the water metabolism would follow, and particularly the effects of adrenocortical and anterior pituitary extracts would have to be considered. A beginning in the investigation of the function of these glands in the newborn has admittedly been made (Moon, 1940; Jailer, 1950; King and Mason, 1950), but the data are as yet too scanty to warrant even tentative conclusions.

This serious gap may serve to emphasize the lack of experimental evidence in this field of neonatal research. We have, one feels, merely reached the stage where the differences between the water and mineral metabolism of the adult and newborn are beginning to be more clearly defined. The analyses of these differences and the evaluation of their clinical importance are to a very large extent a thing of the future.

References

Adolph, E. F. (1943). 'Physiological Regulations.' Lancaster, Pennsylvania.

Alexander, M.B. (1948). *Brit. med. J.*, **2**, 973.

Arnott, G. M., and Young, W. F. (1942). *Lancet*, **i**, 523.

Aschenheim, E. (1919). *Z. Kinderheilk.*, **24**, 281.

Barnett, H. L., Hare, K., McNamara, H., and Hare, R. (1948). *J. clin. Invest.*, **27**, 691.

——, Perley, A. M., and McGinnis, H. G. (1942). *Proc. Soc. exp. Biol. N.Y.*, **49**, 90.

Berliner, R. W., and Kennedy, T. J. (1948). *Ibid.*, **67**, 542.

Brod, J., and Sirota, J. H. (1948). *J. clin. Invest.*, **27**, 645.

Brody, E. B. (1943). *Amer. J. Physiol.*, **139**, 230.

Clark, W. G. (1939). *Proc. Soc. exp. Biol. N.Y.*, **40**, 468.

Dancis, J., Birmingham, J. R., and Leslie, S. H. (1948). *Amer. J. Dis. Child.*, **75**, 316.

Dean, R. F. A., and McCance, R. A. (1947). *J. Physiol., Lond.*, **106**, 431.

——, —— (1949). *Ibid.*, **109**, 81.

Dicker, S. E. (1948). *Ibid.*, **107**, 8.

—— (1950). *Biochem. J.*, **46**, 53.

—— (1951). *Science*, **113**, 187.

——, and Heller, H. (1951). *J. Physiol., Lond.*, **112**, 149.

——, ——, and Hewer, T. F. (1946). *Brit. J. exp. Path.*, **27**, 158.

Elkinton, J. R., and Taffel, M. (1942). *J. clin. Invest.*, **21**, 787.

——, and Winkler, A. W. (1944). *Ibid.*, **23**, 93.

——, ——, and Danowski, T. S. (1948). *Ibid.*, **27**, 74.

Finkelstein, H. (1938). 'Lehrbuch. der Säuglingskrankheiten,' 4th ed. Amsterdam.

Forssman, H. (1945). *Acta Med. Scand.*, Suppl. 159.

Gaisford, W., and Schofield, S. (1950). *Brit. med. J.*, **1**, 1404.

Gamble, J. L. (1947). 'Chemical Anatomy, Physiology and Pathology of Extracellular Fluid.' 5th ed. Harvard Univ. Press.

Gaunt, R. (1944). *Endocrinology*, **34**, 400.

Hallum, J. L. (1941). 'Oedema Neonatorum,' M.D. Thesis. University of St. Andrews. Cited by Young, Hallum, and McCance (1941).

Heller, H. (1944). *J. Physiol., Lond.*, **102**, 429.

—— (1947a). *Ibid.*, **106**, 245.

—— (1947b). *Ibid.*, **106**, 28.

—— (1949). *Ibid.*, **108**, 303.

——, and Smirk, F. H. (1932a). *Ibid.*, **76**, 1.

——, —— (1932b). *Ibid.*, **76**, 23.

——, and Zaimis, E. J. (1949). *Ibid.*, **109**, 162.

Herrington, L. P. (1940). *Amer. J. Physiol.*, **129**, 123.

Jailer, J. W. (1950). *Endocrinology*, **46**, 420.

Joseph, S., Schweizer, M., Ulmer, N. Z., and Gaunt, R. (1944). *Ibid.*, **35**, 338.

Kenney, R. A. (1949). *Acta med. Scand.*, **135**, 172.

Kerpel-Fronius, E. (1932). *Mschr. Kinderheilk.*, **51**, 400.

—— (1940). *Ibid.*, **81**, 294.

King, N. B., and Mason, H. L. (1950). *J. clin. Endocrinol.*, **10**, 479.

Krause, F. (1928). *Z. Biol.*, **87**, 167.

Lasch, W. (1923). *Z. Kinderheilk.*, **36**, 42.

Leaf, A., and Camara, A. A. (1949). *J. clin. Invest.*, **28**, 1526.

McCance, R. A., and Wilkinson, E. (1947). *J. Physiol., Lond.*, **106**, 256.
Moon, H. D. (1940). *Proc. Soc. exper. Biol. N.Y.*, **43**, 42.
Mudge, G. H., Foulks, J., and Gilman, A. (1948). *Ibid.*, **67**, 545.
Nadal, J. W., Pedersen, S., and Maddock, W. G. (1941). *J. clin. Invest.*, **20**, 691.
Pitts, R. F., and Duggan, J. J. (1950). *Ibid.*, **29**, 372.
Rapoport, S. (1947). *Amer. J. Dis. Child.*, **74**, 682.
Rietschel, H. (1934). *Ergebn. inn. Med. Kinderheilk.*, **47**, 185.
Rubin, M. I., Bruck, E., and Rapoport, L. M. (1949). *J. clin. Invest.*, **28**, 1144.
Smith, C. A., Yudkin, S., Young, W., Minkovski, A., and Cushman, M. (1949). *Pediatrics*, **3**, 34.
Smith, H. W. (1937). 'The Physiology of the Kidney.' New York.
Tudvad, F., and Vesterdal, J. (1949). *Acta paediatr., Stockh.*, **37**, 429.
West, J. R., Smith, H. W., and Chasis, H. (1948). *J. Pediat.*, **32**, 10.
Williams, R. H., and Henry, C. (1947). *Ann. intern. Med.*, **27**, 84.
Winkler, A. W., and Smith, P. K. (1942). *Amer. J. Physiol.*, **138**, 94.
Verney, E. B. (1948). *Brit. med. J.*, **2**, 119.
Young, W. F., Hallum, J. L., and McCance, R. A. (1941). *Archives of Disease in Childhood*, **16**, 243.
Young, W. F., and McCance, R. A. (1942). *Ibid.*, **17**, 65.

CHEMICAL DEVELOPMENT *IN UTERO*

BY

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In spite of the spectacular advances in scientific medicine which we have witnessed in the last 20 years, there is still a need for information about a number of fundamental, if quite elementary, matters. One of these is the chemical composition of the human body. A knowledge of the quantitative make-up of the bodies of men, women, and children in both health and disease is of value for investigations of the most diverse types, but much of the information available is the result of guess work rather than chemistry. It is proposed to describe the results of an attempt to fill some of the gaps in our knowledge.

Von Bezold (1857, 1858) was the first to make an analysis of a human foetus. It weighed 523 g., and he determined both organic and inorganic constituents. During the next 50 years a number of analyses were made, mostly in Germany and France, though one paper from Italy and one from Holland were published. Fehling (1877) studied 21 foetuses varying in weight from 1 to 3,294 g. He was interested only in the amounts of water, nitrogen, and fat, but most workers included inorganic constituents in their analyses (Brubacher, 1891; Giacosa, 1895; Michel, 1899; Hugounenq, 1899, 1900a, b; de Lange, 1900; Camerer, 1900a, b, 1902; Söldner, 1903; Steinitz, 1904; Langstein and Edelstein, 1917). Further data have been provided by Givens and Macy (1933), who analysed 25 foetuses of various ages for water, ash, calcium, and magnesium, and Iob and Swanson (1934), who estimated water, fat, nitrogen, sodium, potassium, calcium, magnesium, phosphorus, and chloride in 17 foetuses weighing between 1·7 and 2,915 g. Macy and Hunscher (1934), Coons, Schiefelbusch, Marshall, and Coons (1935) and Garry and Stiven (1936) took all these figures for the chemical composition of the human foetus into consideration in making their calculations of the dietary requirements of the mother during pregnancy and lactation.

Several studies of the chemical composition of the human placenta have been recorded. Full-term placentae have been analysed for water, nitrogen, fat, and ash by Higuchi (1909) and by Pratt, Kaucher, Richards, Williams and Macy (1946). The amino-acids were studied by Koelker and Slemons (1911) and the different fatty constituents by Pratt, Kaucher, Moyer, Richards, and Williams (1946). Masters and Clayton (1940) were particularly interested in the amount of calcium in the placenta at different stages of maturity and Hilgenberg (1930) in the concentration of iron. These workers confined their studies to the placenta, and no parallel investigation of foetuses and placentae ever appears to have been made.

In the present study 19 human foetuses and full-term infants have been analysed for nitrogen, fat. sodium, potassium, calcium, magnesium, phosphorus, iron, copper, and zinc, and the iodine in a number of thyroid glands was determined. Placentae from 12 of the foetuses were also analysed.

Material

Thirteen immature foetuses, two of which were twins, six stillborn infants weighing more than 3,000 g., and 12 placentae were obtained through the courtesy of the staff of Addenbrooke's Hospital and the County Maternity Hospital, Mill Road, Cambridge. Details as to foetal ages, sex and weights, and the cause of death are given in Table 1. Age was assessed by measurement of footlength (Streeter, 1920), but this and all other methods are acknowledged to be uncertain, and the chemical findings have therefore all been related to body weight. The livers and spleens were analysed separately from the rest of the body. The thyroid glands of 16 of the foetuses were sent by post to Miss B. W. Simpson, Rowett Research Institute, Aberdeen, for the determination of iodine. The amount of iodine was also determined in the thyroid glands from 16 children between birth and one year, and from 10 older children and three adults. These glands were removed at post-mortem examination at Addenbrooke's Hospital.

Preparation for Analysis. The bodies were weighed as soon after delivery as possible, and dissected on an enamel tray so that no blood was lost. The livers and spleens were removed and washed with distilled water, and the washings were added to the main sample. The thyroid glands were dissected out and weighed. The bodies, together with all the washings, were brought into solution with HCl as described by Venn, McCance, and

TABLE 1

DESCRIPTION OF MATERIAL

Foetus No.	Sex	Approximate Foetal Age (weeks)	Weight (g.)	Age of Mother (years)	Parity of Mother	Cause of Death
1 (P)	M.	17	225	26	?	Hysterotomy
2 and 3 (twins) (P)	Both M.	17	227 247	17½	1	Inevitable abortion
4 (P)	M.	19	286	?	?	Ante-partum haemorrhage
5 (P)	F.	22	400	37	6	Habitual abortion
6	M.	22	478	21	1	Hysterotomy
7 (P)	M.	23	673	36	1	Hysterotomy
8	M.	24	787	39	?	Hysterotomy and ovariectomy for carcinoma of ovaries
9 (P)	M.	26	911	34	7	Hysterotomy
10 (P)	F.	30	1,718	36	4	Surgical induction
11 (P)	M.	32	1,966	41	3	Placenta praevia
12	F.	33	2,295	24	?	Ante-partum haemorrhage
13	M.	34	2,652	35	4	,, ,,
14 (P)	F.	34	3,090	21	1	Breech presentation
15 (P)	F.	37	3,767	23	1	Eclampsia
16	M.	37	3,105	?	?	Unknown
17	F.	39	3,050	?	?	,,
18 (P)	M.	40	4,375	36	5	Hydrocephalic
19 (P)	M.	40	3,994	31	6	Placenta praevia

(P) = placenta analysed.

Widdowson (1947). The livers and spleens were weighed and chopped up finely with a stainless steel knife. Weighed portions were taken for the determination of inorganic iron, and for ashing before the estimation of the metallic constituents. The remainder, a known proportion of the whole, was digested with HCl and used for the determination of nitrogen, phosphorus, and fat.

The placentae were drained as free from blood as possible, rapidly washed in distilled water and dried on blotting paper before being weighed. They were brought into solution in HCl and subsequently treated exactly as the other material.

Chemical Methods. The chemical methods used for the determination of nitrogen, fat and inorganic constituents are described by Spray and Widdowson (1950). The method of Harvey (1935) was used for the iodine estimations.

The Chemical Composition of the Human Foetus and Full-term Infant

Protein, Fat, and Water. Fig. 1 shows the total amounts of fat and protein in each individual foetus, Fig. 2 the percentages of these substances in the whole body, and Fig. 3 the percentages of protein and water calculated on a fat-free basis. These results emphasize (*a*) the enormous increase in the proportion of fat, from less than 1% in the early stages to over 28% in one full-term infant; and (*b*) the decrease in the proportion of water and the corresponding increase in the proportion of protein when expressed on a fat-free basis. If the protein is calculated as a percentage of the whole body (Fig. 2), the concentration increases till the foetus weighs about 3,000 g., and then decreases again,

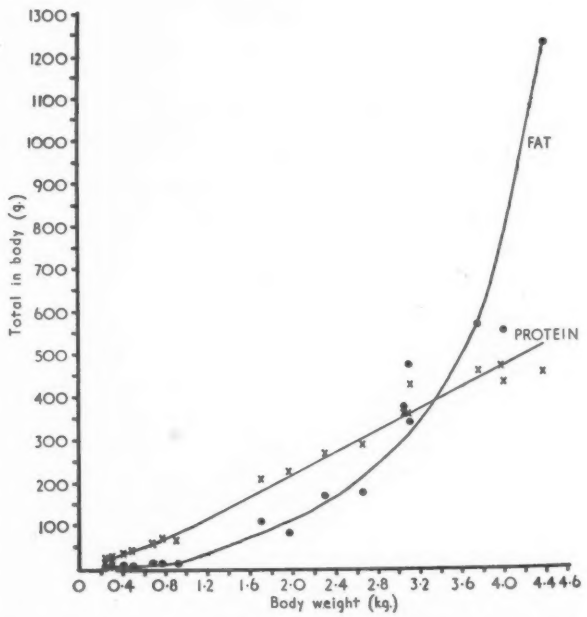

FIG. 1.—Total amounts of fat and protein in the foeta bodies.

because from that stage onwards the increase in fat is greater than the decrease in water. The foetus

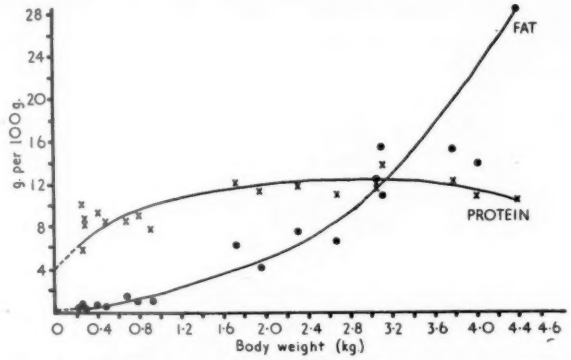

FIG. 2.—Percentage of fat and protein in the foetal bodies.

begins to lay down fat when it weighs 800-1,000 g. By the time it is 3,000 g. the amount of fat in its body is approximately equal to the amount of protein. Thereafter the fat increases very rapidly indeed, so that a baby with a birth weight of 4,000 g. is likely to have about 400 g. more fat than one which weighed 3,000 g. although it would only contain about 100 g. more protein.

Previous workers who have determined the protein, fat, and water have devoted their attention mainly to foetuses in the early stages of development. For example, of the 21 foetuses analysed by Fehling (1877), 17 weighed less than 1,000 g., and five of the seven studied by Michel (1899) were under 700 g. in weight. In fact, only five foetuses weighing more than 3,000 g. ever appear to have been analysed for these constituents, and the heaviest of these was 3,360 g. Of the present series, six weighed more than 3,000 g. and three more than 3,360 g. While the older work, therefore, is useful in indicating the composition of the foetus during the first few months of intra-uterine life, the present study gives a better picture of the chemical make-up of the full-term baby than any previously made.

The convention in the past has always been to make an assessment of the foetal age and to relate the chemical composition of the body to it. If the results of previous workers for water, protein, and fat are plotted against weight as in the present series (Figs. 1, 2 and 3), curves very similar in shape are obtained in the early stages. The smallest embryos ever analysed, weighing only a gram or so, contained about 4% of protein, 0·4% of fat, and 95·5% of water, and the curves in Fig. 2 have been extended to include these values. On the other hand it appears that the figure of 12% given by Shohl (1939) for the average percentage of fat in a baby at birth is too low. Shohl used all the available data in arriving at this figure, but the weight of his 'newborn' infant, 2·9 kg. (6 lb. 6 oz.), is rather low for the average weight of a full-term baby. Five of the six foetuses weighing more than 3,000 g. in the present study had more than 12% of fat in their bodies.

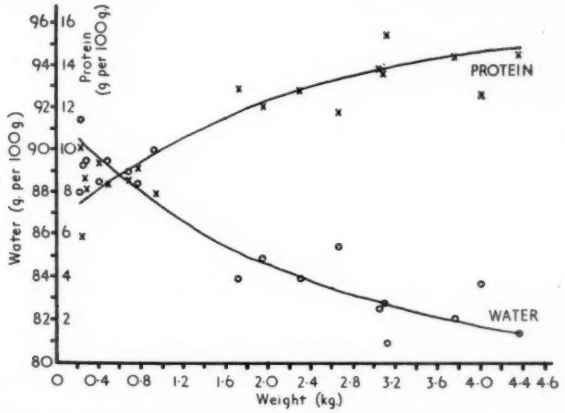

FIG. 3.—Protein and water (g. per 100 g. of fat-free body tissue).

Sodium and Potassium. It is now generally taught that the proportion of sodium in the fat-free body tissue decreases during growth, both before birth and afterwards, and that this fall is brought about by a decrease in the fraction of the body occupied by extracellular fluids (Shohl, 1939). In Fig. 4 are shown the total amounts of sodium and potassium in the foetuses analysed in the present investigation, and in Fig. 5 the amounts of these elements per 100 g. of fat-free body tissue. The concentration of sodium was rather variable. It tended to decrease in the early stages, but from the time the foetus weighed 2,000 g. it was approximately constant at about 220-225 mg. per 100 g., and this

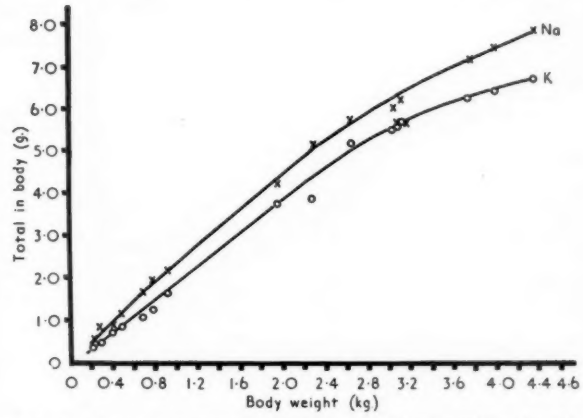

FIG. 4.—Total amounts of sodium and potassium in the foetal bodies.

was also the value found for the concentration of sodium in the fat-free tissue of the human adult

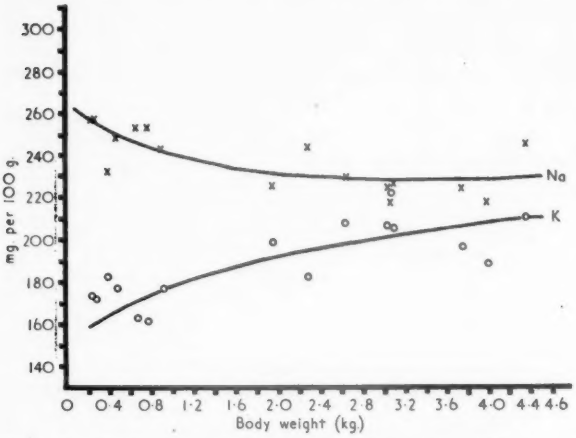

FIG. 5.—Sodium and potassium (mg. per 100 g. of fat-free body tissue).

(Widdowson, McCance, and Spray, 1950). These results seem to be a direct contradiction of the view which is commonly held at the present time. There is no doubt that the proportion of extracellular fluids does fall (Fellers, Barnett, Hare, and McNamara, 1949), and with it the proportion of extracellular fluid sodium in the body. It is quite clear from the work of Harrison, Darrow, and Yannet (1936), however, that about 50% of the sodium in the body of the adult monkey, dog, and rabbit is in the skeleton, and that half of this is present as an insoluble or undissociated compound which contributes little if anything to the osmotic pressure of skeletal water. The same is probably true of the human adult, and Widdowson *et al.* (1950) have obtained some direct confirmatory evidence. Harrison *et al.* made some calculations from the data of Iob and Swanson (1934) of the total and extracellular sodium in the bodies of human foetuses of various weights, and have shown that, whereas in a foetus weighing 340 g. the extracellular sodium accounts for 97·5% of the total sodium in the body, by the time the foetus weighs 2,970 g., only 76% of the sodium in the body is in the extracellular fluids. It appears that, from the seventh month of prenatal life onwards, the fall in the proportion of extracellular sodium is just about counterbalanced by the increase in the amount of sodium being deposited in the skeletal tissues.

The concentration of potassium in the fat-free body tissue increased during intra-uterine life, but it was always lower than the concentration of sodium, and the infant at full term contained about 200-210 mg. of potassium per 100 g. of fat-free body tissue. Shohl's (1939) figure for the concentration of potassium in the fat-free tissue of a newborn baby is 190 mg. per 100 g. but it is probable that his newborn baby was not really mature. Nearly all the potassium in the human body is in the cells, and the concentration in the whole body is what one would expect from a knowledge of the volume of intracellular water and the concentration of potassium in it (Harrison *et al.*, 1936). Thus the concentration of potassium in the whole body increases in proportion to the increase in cell mass and the value for the concentration of potassium in the human adult (Widdowson *et al.*, 1950) is considerably higher than the present figure for the infant at term.

Calcium, Phosphorus, and Magnesium. Fig. 6

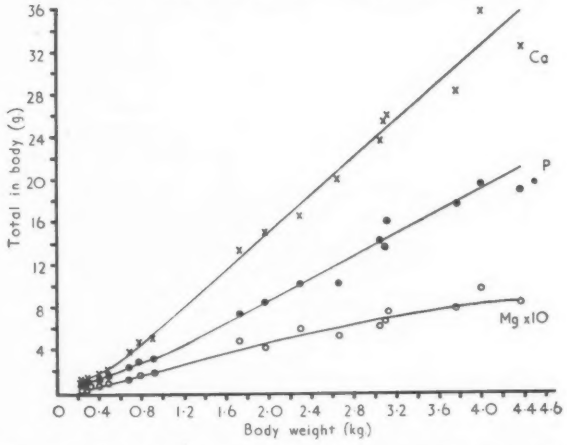

FIG. 6.—Total amounts of calcium, magnesium, and phosphorus in the foetal bodies.

shows the total amounts of calcium, phosphorus, and magnesium in the foetal bodies, and Fig. 7 the percentages of these elements on a fat-free basis. The absolute amounts of all three elements showed a steady increase with increasing weight so that the full-term infants contained 20 or 30 times more of each than the foetuses weighing 225 g. or so. The percentages also increased, the concentration of calcium at full term being rather more than twice, and of phosphorus a little less than twice as high as it was in the smallest foetuses examined. The concentration of magnesium rose in the early stages, but remained almost constant in foetuses weighing 2,000 g. and over.

Early investigators who determined the calcium, magnesium, and phosphorus in the human foetus did not always give the percentage of fat, so their figures cannot be compared with those shown in Fig. 7. If the results previously published for the total amounts of calcium, magnesium, and phosphorus in human foetuses are plotted against body weights, curves similar to those in Fig. 6 are obtained, but

during the past 30 years only one foetus weighing more than 1,615 g. has been analysed. Coons *et al.*

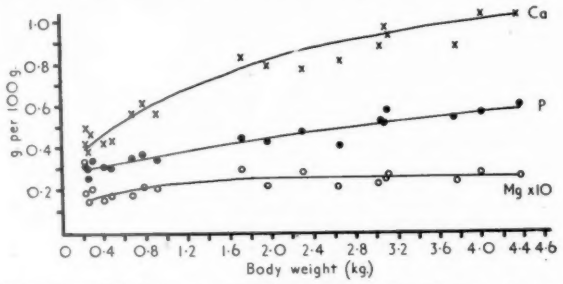

FIG. 7.—Calcium, magnesium, and phosphorus (g. per 100 g. of fat-free body tissue).

(1935) and Garry and Stiven (1936) took Michel's (1899) data for a foetus weighing 3,335 g. to represent the composition of the human infant at term, but Michel's figures for all three elements are considerably higher than those shown in Fig. 6 for a foetus of a similar size. Booher and Hansmann (1931) analysed the tibiae of newborn infants and found the proportion of calcium in these bones to be nearly constant when expressed on a dry fat-free basis, irrespective of the calcium intake or age of the mother. They suggested that the composition of the skeleton is constant, and that variations only appear when the results for calcium are expressed as a percentage of the whole body.

It is due to the progressive calcification of the bones, which have a Ca/P ratio of over 2 that the Ca/P ratio of the whole body tends to rise as development proceeds, particularly during the first seven months or so of intra-uterine life (Fig. 8),

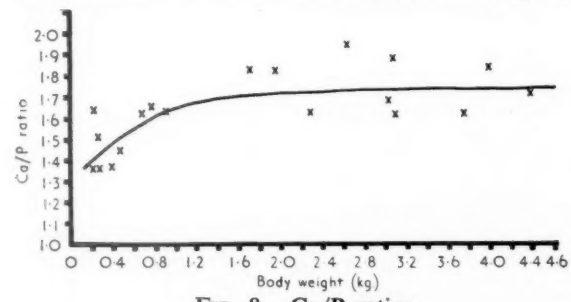

FIG. 8.—Ca/P ratios.

but three foetuses which weighed 600-900 g. had ratios as high as two others which weighed over 3,000 g. Iob and Swanson's (1934) ratios were equally irregular. The ratio at term is probably between 1·7 and 1·8, and this was the value found by Widdowson *et al.* (1950) for the human adult.

Iron, Copper, and Zinc. The total amounts of iron and zinc in the whole foetal bodies are shown in Fig. 9 and of copper in Fig. 10. The quantity of iron was rather variable in the full-term infants, but no figure approaching the 937 mg. given by Garry and Stiven (1936) was obtained. Very few whole bodies have been analysed for iron in the past. Hugounenq (1899) was particularly interested in this element and his results fit in much better with the present series than those of Camerer (1902). Camerer, whose values are higher than our own, himself suspected that his samples were contaminated with iron. Fullerton (1937) assessed the

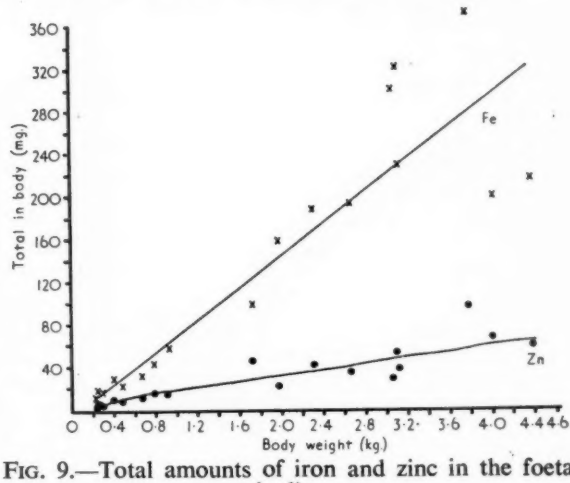

FIG. 9.—Total amounts of iron and zinc in the foetal bodies.

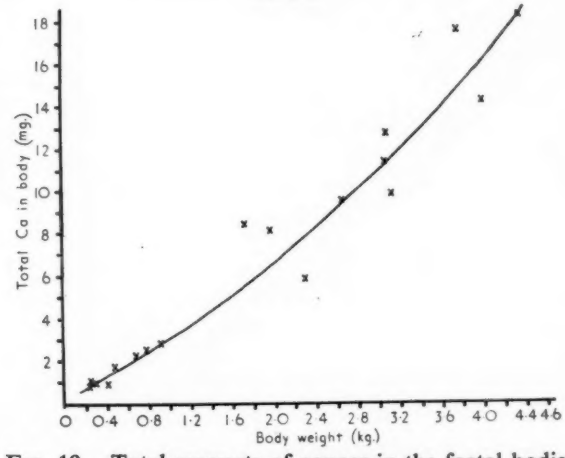

FIG. 10.—Total amounts of copper in the foetal bodies.

amount of iron in a full-term baby from published figures for blood volumes and haemoglobin levels, and his estimate was 450 mg. This is higher than any of the present series and there is reason to believe that it is too high (McCance and Widdowson, 1951). The average for the six infants weighing more than 3,000 g. in this investigation was 273 mg. How this lower value for the iron in the full-term foetus affects any theory about the development of suckling anaemia is discussed by McCance and Widdowson (1951).

No information about the amounts of copper and zinc in foetal bodies has hitherto been published.

The quantities of iron and zinc per 100 g. of fat-free body substance are given in Fig. 11, and

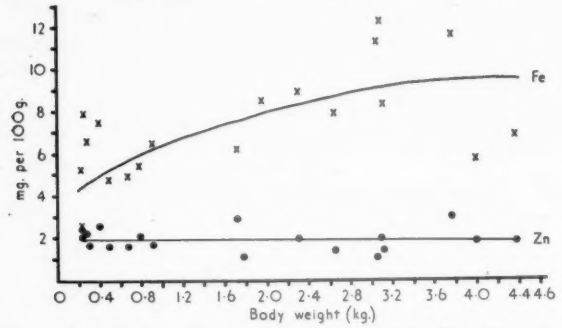

FIG. 11.—Iron and zinc in the foetal bodies (mg. per 100 g. of fat-free body tissue).

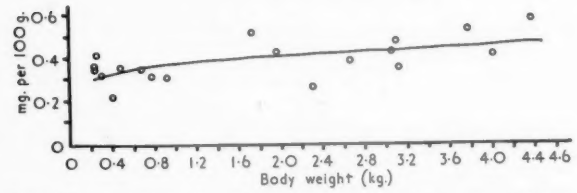

FIG. 12.—Copper in the foetal bodies (mg. per 100 g. of fat-free body tissue).

of copper in Fig. 12. The concentrations of iron and copper tended to be a little higher in the larger foetuses, but the two biggest contained no more iron per 100 g. than some of the smallest ones. This implies that no large store of iron is accumulated by the human foetus shortly before birth (McCance and Widdowson, 1951). The 'concentration' of zinc did not change throughout intrauterine life and the increase in total amount exactly paralleled the increase in body weight.

Table 2 shows the concentration of inorganic iron, copper, and zinc in the liver and spleen, and the percentage of the total amount in the body present in these organs. The results were irregular, but of the same order for iron and copper whatever the age and size of the foetus. The liver and spleen always contained about the same proportion of the body's iron, copper, and zinc. Roughly speaking, about one half of the copper, one quarter of the zinc, and one eighth of the iron in the body was found in these two organs. If the results shown in Figs. 11 and 12 are compared with the values given in Table 2 it will be seen that the concentration of iron was about twice, the concentration of zinc about 10 times, and that of copper 20 or 30 times as high in the liver and spleen as in the body as a whole.

Several workers have analysed the livers of stillborn infants for inorganic iron or for total iron in the blood-free organ (Adler and Adler, 1931; Gladstone, 1932; Toverud, 1935; Schairer and Rechenberger, 1943). Their assessments ranged from about 30 to 60 mg. of iron in the whole liver. Stearns and McKinley (1937) suggested that the amount might be much less if the mother's diet had been deficient in iron. The present values for the foetuses weighing more than 3,000 g. varied from 11·5 to 51·4 mg. Brückmann and Zondek (1939) determined both iron and copper in the livers of five newborn infants. Their findings for iron varied from 8·8 to 58·8 mg. per 100 g. and for copper from 1·2 to 6·9 mg. per 100 g. It will be seen from

TABLE 2

DISTRIBUTION OF INORGANIC FE, CU, AND ZN IN THE FOETAL BODIES

Weight of Foetus (g.)	Distribution in Liver and Spleen (mg. per 100 g.)			Percentage of the Body's Fe, Cu, and Zn in Liver and Spleen		
	Inorganic Fe	Cu	Zn	Inorganic Fe	Cu	Zn
225	—	—	32·9	—	—	58
227	—	2·03	11·9	—	17	17
247	—	1·53	10·8	—	14	21
286	20·4	4·12	17·2	16	66	53
673	8·5	4·07	17·7	7	48	43
787	6·8	5·28	14·6	4	46	20
911	30·0	4·62	20·7	19	62	51
1,718	—	8·70	19·1	—	69	27
1,966	20·0	4·80	8·7	14	64	43
2,295	19·9	2·58	10·0	10	43	23
3,050	37·0	2·42	6·1	17	29	28
3,090	25·5	3·92	5·1	15	58	18
3,105	10·4	3·83	5·4	5	46	17
3,994	21·1	4·60	9·0	19	58	24
4,375	16·7	6·00	8·7	14	61	27

Table 2 that these figures are of the same order as our own. The amount of zinc in the human liver does not seem to have been investigated hitherto.

Iodine in the Thyroid Gland

The results of the determinations of iodine are set out in Table 3. The concentration of iodine in the thyroid gland was variable from one individual to another, but there was an increase with increasing age. The average for foetuses weighing less than 1,000 g. (omitting the pair of twins) was 2·4 mg. per 100 g. and for those weighing more than 1,000 g. was 3·1 mg. per 100 g. The average value for the children below one year was 7·8, for the older children 19·2 and for the three adults 41·7 mg. per 100 g. Koneff, Nichols, Wolff, and Chaikoff (1949) have shown that the concentration of iodine in the thyroid of the foetal calf increases progressively with age and have postulated that the foetal thyroid acquires an increased capacity for collecting and storing iodine. The present findings for the human foetus would not be a contradiction of this, and the same process may go on in extra-uterine life.

One point of interest about the present series of thyroids from full-term infants is their size. The human thyroid generally weighs 1 g. at birth (B. W. Simpson, personal communication), though Ekholm and Niemenera (1950), working in Finland, reported weights ranging from 1·65 to 3·18 g. for the thyroid glands of foetuses weighing between 1,250 and 2,500 g. These authors emphasize the great variability in the weights of the thyroids of foetuses of the same size. All six of the foetuses in the present series weighing more than 2,000 g. had thyroids weighing more than 1 g. and the glands of four of them weighed more than 2 g. One of the newborn infants had a grossly enlarged thyroid, weighing 8·6 g., and a girl of 4 also had one which was abnormally heavy (6·9 g.). Both these thyroids contained very low ' concentrations ' of iodine, and there was less iodine in these glands than in those of other children of similar age. All the foetuses and children with the enlarged glands came from Cambridge or the country nearby, and the material was collected during the years 1944 and 1945.

Composition of the Human Placenta

Table 4 shows the percentage composition of the 12 placentae which were analysed. Figures for iron have been omitted because, although most of the blood was removed, it is certain that some still remained, and the values for iron would have been greatly influenced by the amount of residual blood.

The placental weights did not necessarily follow the foetal weights, and the largest foetus had a

TABLE 3

ANALYSES OF IODINE IN THE THYROID GLAND

	Foetuses			Infants under 1 year				Children over 1 year and Adults			
Approx. Foetal Age (weeks)	Body weight (g.)	I_2 mg. per 100 g. Thyroid	Total I_2 in Thyroid (μg.)	Age	Sex	I_2 mg. per 100 g.	Total I_2 in Thyroid (μg.)	Age (years)	Sex	I_2 mg. per 100 g. Thyroid	Total I_2 in Thyroid (μg.)
Twins											
17	227	0·8	0·29	Newborn	F.	14·0	134	1	F.	12·0	156
17	247	0·04	0·01	,,	M.	4·0	46	1½	M.	14·0	321
19	286	4·0	6·8	,,	F.	0·3	26	2	M.	12·0	312
22	400	1·4	2·5	5 days (premature)	M.	6·0	51	3½	F.	13·0	460
22	478	1·5	3·8	6 days (premature)	F.	8·0	67	4	M.	39·0	940
23	673	6·0	12·3	15 days	F.	6·0	107	4	F.	2·0	139
24	787	0·9	4·8	24 days	M.	13·0	77	5	F.	34·0	820
26	911	0·5	3·2	2 months	F.	2·7	36	6	M.	15·0	805
30	1,718	3·0	24·3	2 ,,	M.	13·0	260	6	F.	13·0	597
32	1,966	0·6	5·9	2 ,,	F.	7·6	69	12	F.	38·0	2,810
33	2,295	2·0	45·3	2½ ,,	M.	18·0	214	21	M.	27·0	5,680
34	2,652	1·2	24·9	2½ ,,	M.	9·0	112	27	F.	40·0	5,050
34	3,090	8·0	131·0	3 ,,	?	9·6	234	31	M.	58·0	17,300
37	3,767	3·3	111·4	4 ,,	M.	5·0	140				
40	3,994	0·3	7·9	6 ,,	F.	3·0	57				
40	4,375	6·0	105·2	7 ,,	M.	6·0	79				

TABLE 4

COMPOSITION OF HUMAN PLACENTAE

Approximate foetal age in weeks	17	17 (Twins)	19	22	23	26	30	32	34	37	40	40
Weight of placenta (g.)	140	488	329	271	165	275	570	451	545	927	806	616
Weight of foetus (g.)	225	227+ 247	286	400	673	911	1,718	1,966	3,090	3,767	3,994	4,375
Water (g. per 100 g.)	88·5	87·8	90·5	85·1	85·3	85·7	86·0	85·1	83·4	88·8	88·1	84·9
Protein ,,	9·7	10·7	8·0	13·1	12·5	12·4	12·1	13·5	14·3	9·9	10·0	13·4
Fat ,,	0·7	0·6	0·5	0·8	0·9	0·7	1·0	0·6	0·8	0·5	1·0	0·6
Na (mg. per 100 g.)	265	251	248	232	282	225	225	190	225	148	194	207
K ,,	139	149	137	176	163	167	172	131	158	149	121	193
Ca ,,	20·9	28·2	20·1	17·8	28·8	26·0	25·1	29·2	151·5	27·0	48·3	40·0
Mg ,,	7·4	6·2	7·5	6·1	8·4	7·6	7·9	10·0	11·6	6·0	7·4	8·3
P ,,	98	80	60	89	124	107	98	92	187	85	113	132
Cu ,,	0·17	0·20	0·13	0·16	0·11	0·18	0·14	0·11	0·17	0·13	0·10	0·14
Zn ,,	0·96	0·85	1·19	1·20	1·10	1·07	0·79	0·46	1·28	1·00	0·95	1·12

placenta which was very little heavier than that of a foetus weighing less than half as much. Other workers (Pratt *et al.* 1946) also found that weights of foetuses and placentae did not always run together.

The placenta is a very watery organ, and the percentage of water does not appear to be less at full term than it is earlier in pregnancy. Pratt *et al.* (1946), who analysed nine full-term placentae, found the moisture to vary from 85 to 94% with an average of 87%. These figures agree very well with our own. The proportions of protein and fat also remained of the same order throughout. The protein and fat in the placentae of the four foetuses weighing more than 3,000 g. averaged 11·9% and 0·7% respectively; the corresponding figures for the other placentae were 11·5 and 0·7%.

The concentration of calcium in the placentae of the smaller foetuses was similar to that found by Masters and Clayton (1940). There was one high figure in the series, 151·5 mg. per 100 g., from a 34-week pregnancy, and this placenta would probably have appeared calcified on x-ray examination. There was possibly an increase in the concentration of phosphorus with increasing age, but on the whole the mineral make-up altered little and, except for the calcification of the arteries, which is probably a sign of degeneration, it is clear that no changes in the composition of the placenta take place which are at all comparable with the alterations in the composition of the developing foetus.

At the seventeenth to the nineteenth week of pregnancy the foetus and its placenta were of approximately equal weight, and both contained similar amounts of nitrogen, fat, and potassium. The foetus contained more of all the other constituents, two to five times as much magnesium, phosphorus, copper, and zinc and 20 or 30 times as much calcium. During the last four months the foetus grows much more rapidly than the placenta so that at term it weighs five or six times as much. The concentrations of nitrogen and potassium remained very similar in both. At full term the concentrations of magnesium, phosphorus, copper, and zinc were two to four times as high in the foetus as in the placenta, the concentration of calcium between five and 30 times and of fat 25 times as high.

Discussion

From the results which have been obtained an estimate has been made of the probable composition of the body of a premature baby weighing 1,500 g. (3½ lb.) and of one weighing 2,500 g. (5½lb.), compared with that of a full-term infant weighing 3,500 g. (7½ lb.). The values are set out in Tables 5 and 6. The outstanding deficiency of the premature baby is one of fat. The baby weighing 1,500 g. contains only one-eighth as much fat as a full-term infant. Most mammalian species are born with only 1-2% of fat in their bodies, and the full-term human baby represents the exception in chemical composition rather than the rule. Widdowson (1950) has discussed various reasons for this difference in the composition at birth. The lack of subcutaneous fat in premature babies is, of course, well known to those responsible for their care

(Crosse, 1945) and there is no doubt that the layer of fat beneath the skin is of great value to the human infant as an insulation against loss of heat. It is interesting to consider how the newborn of other species manage to survive without any subcutaneous fat at all (Thomas, 1911; Widdowson, 1950).

The values given in Table 5 represent the percentage composition of the whole body, and not as in Figs. 3, 5, 7, and 11, the amounts per 100 g. of fat-free body tissue. Since the proportion of fat in the body is greater the more mature the foetus, the lower the concentration of all the other constituents will tend to be when expressed as a percentage of the whole body in comparison with the same data expressed on a fat-free basis. This is well illustrated by a comparison of the curves for protein in Figs. 2 and 3.

TABLE 5

COMPARISON BETWEEN PERCENTAGE COMPOSITION OF PREMATURE BABIES AND A FULL-TERM INFANT

	Premature (1,500 g.)	Premature (2,500 g.)	Full Term (3,500 g.)
Protein (g. per 100 g.)	11·6	12·4	12·0
Fat ,,	3·5	7·6	16·2
Water ,,	82·5	77·3	68·8
Na (g. per 100 g.)	0·23	0·21	0·19
K ,,	0·19	0·19	0·17
Ca ,,	0·68	0·76	0·81
Mg ,,	0·023	0·024	0·022
P ,,	0·37	0·43	0·46
Fe (mg. per 100 g.)	7·1	7·4	7·5
Cu ,,	0·32	0·35	0·39
Zn ,,	1·7	1·6	1·5

TABLE 6

TOTAL AMOUNTS OF VARIOUS CONSTITUENTS IN THE BODIES OF PREMATURE BABIES COMPARED WITH THOSE IN A FULL-TERM BABY

	Premature (1)	Premature (2)	Full Term	Premature (1) as % of Full-term	Premature (2) as % of Full-term
Weight (g.)	1,500	2,500	3,500	43	72
Protein (g.)	160	290	415	39	70
Fat (g.) ..	60	200	470	13	43
Na (g.) ..	3·50	5·35	6·75	52	80
K (g.) ..	2·80	4·70	6·00	47	78
Ca (g.) ..	10·2	19·0	28·2	36	68
Mg. (g.) ..	0·35	0·60	0·76	46	79
P (g.) ..	5·6	10·8	16·2	35	67
Fe (mg.) ..	106	184	262	41	70
Cu (mg.)	4·8	8·8	13·7	35	64
Zn (mg.) ..	26·0	40·0	53·0	49	76

The concentrations of protein, potassium, magnesium, and iron in the whole body are about the same whether the infant weighs 1,500 g. or 3,500 g., and the proportion of the body occupied by cellular tissue, therefore, probably remains fairly constant at this stage of development. As the foetus lays down fat the extracellular fluids form a smaller and smaller fraction of the body and in spite of the deposition of sodium in the skeleton, the concentration of sodium in the whole body falls.

A premature baby not only has less calcium and phosphorus in its whole body than one which is born at full-term, but it also has less per 100 g. body weight in spite of the fact that the full-term baby has so much more fat. The premature baby also appears to have a slightly smaller concentration of copper.

Summary

Thirteen immature foetuses and six stillborn infants weighing more than 3,000 g. have been analysed for nitrogen, fat, sodium, potassium, calcium, magnesium, phosphorus, iron, copper, and zinc, and the iodine in the thyroid glands was determined. The placentae of 12 of the foetuses and infants were also investigated.

The foetus begins to lay down fat when it weighs 800-1,000 g., and by the time it weighs 3,000 g. the amount of fat in its body is approximately equal to the amount of protein (12%). After this the fat increases much more rapidly than the protein, and one stillborn infant which weighed 4,375 g. contained 28% of fat.

The concentration of sodium per 100 g. of fat-free body tissue decreased until the foetal weight was about 2,000 g., and then remained constant until term. The value reached was the same as in adult life. The concentration of potassium in the fat-free body tissue increased throughout intrauterine life, but the concentration in the whole body altered little from the time the foetus began to lay down fat.

The concentration of calcium and phosphorus increased with increasing weight, so that the percentage of calcium at full term was rather more than twice and of phosphorus a little less than twice as high as it was in the foetuses weighing 200-300 g.

The percentage of iron and copper in the foetus increased with development while that of zinc did not change. The liver and spleen contained about one-half of the copper, one-quarter of the zinc, and one-eighth of the iron in the whole body.

The concentration of iodine in the thyroid appeared to increase during foetal life and after, and in the thyroids from three adults was about 20 times as high in those from the immature foetuses.

At the seventeenth to nineteenth week of pregnancy the foetus and its placenta were of approximately equal weight, and contained similar amounts of nitrogen, fat, and potassium. During the last four months the foetus grows much more rapidly so that at full term it weighed five or six times as much as its placenta. The "concentrations" of nitrogen and potassium were similar in both, but those of fat, calcium, magnesium, phosphorus, copper, and zinc were all higher in the foetus than in its placenta.

We should like to take this opportunity of thanking Professor R. A. McCance for his wise encouragemenl throughout the investigation. We are also very grateful to Dr. R. F. A. Dean for his help in obtaining the bodies for analysis, and to Miss B. W. Simpson for making the iodine analyses.

References

Adler, K., and Adler, M. (1931). *Z. Geburtsh. Gynäk.*, **101,** 128.

Bezold, A. von (1857). *Z. wiss. Zool.*, **8,** 487.

—— (1858). *Ibid.*, **9,** 240.

Boohor, L. E., and Hansmann, G. H. (1931). *J. biol. Chem.*, **94,** 195.

Brubacher, H. (1891). *Z. Biol.*, **27,** 517.

Brückmann, G., and Zondek, S. G. (1939). *Biochem. J.*, **33,** 1845.

Camerer, W. Jr. (1900a). *Z. Biol.*, **39, 173.**

—— (1900b). *Ibid.*, **40,** 529.

—— (1902). *Ibid.*, **43,** 1.

Coons, C. M., Schiefelbusch, A. T., Marshall, G. B., and Coons, R. R. (1935). *Oklahoma Agric. Mech. Coll., Agric. Exp. Sta. Bull.*, No. 223.

Crosse, V. M. (1945). 'The Premature Baby.' London.

Ekholm, E., and Niemenera, K. (1950). *Acta. Paediatr.*, **39,** 67.

Fehling, H. (1877). *Arch. Gynäk.*, **11,** 523.

Fellers, F. X., Barnett, H. L., Hare, K., and McNamara, H. (1949). *Pediatrics*, **3,** 622.

Fullerton, H. W. (1937). *Archives of Disease in Childhood*, **12,** 91.

Garry, R. C., and Stiven, D. (1936). *Nutr. Abst. Rev.*, **5,** 855.

Giacosa, G. (1895). *Arch. ital. Biol.*, **22,** 252.

Givens, M. H., and Macy, I. G. (1933). *J. biol. Chem.*, **102,** 7.

Gladstone, S. A. (1932). *Amer. J. Dis. Child.*, **44,** 81.

Harrison, H. E., Darrow, D. C., and Yannet, H. (1936). *J. biol. Chem.*, **113,** 515.

Harvey, C. O. (1935). *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 201.

Higuchi, S. (1909). *Biochem. Z.*, **15,** 95.

Hilgenberg, F. C. (1930). *Z. Geburtsh. Gynäk.*, **98,** 291.

Hugounenq, M. L. (1899). *J. Physiol. Path. gén.*, **1,** 703.

—— (1900a). *Ibid.*, **2,** 1.

—— (1900b). *Ibid.*, **2,** 509.

Iob, V., and Swanson, W. W. (1934). *Amer. J. Dis. Child.*, **47,** 302.

Koelker, A. H., and Slemons, J. M. (1911). *J. biol. Chem.*, **9,** 471.

Koneff, A. A., Nichols, C. W., Wolff, J., and Chaikoff, I. L. (1949). *Endocrinology*, **45,** 242.

Lange, C. de (1900). *Z. Biol.*, **40,** 526.

Langstein, L., and Edelstein, F. (1917). *Z. Kinderheilk.*, **15,** 49.

McCance, R. A., and Widdowson, E. M. (1951). *J. Physiol.* **112,** 450.

Macy, I. G., and Hunscher, H. A. (1934). *Amer. J. Obstet. Gynec.*, **27,** 878.

Masters, M., and Clayton, S. G. (1940). *J. Obstet. Gynaec.*, **47,** 437.

Michel, C. (1899). *C.R. Soc. Biol., Paris*, **51,** 422.

Pratt, J. P., Kaucher, M., Moyer, E., Richards, A. J., and Williams, H. H. (1946). *Amer. J. Obstet. Gynec.*, **52,** 665.

Pratt, J. P., Kaucher, M., Richards, A. J., Williams, H. H., and Macy, I. G. (1946). *Ibid.*, **52,** 402.

Schairer, E., and Rechenberger, J. (1943). *Z. Kinderheilk.*, **64,** 255.

Shohl, A. T. (1939). 'Mineral Metabolism.' New York.

Söldner (1903). *Z. Biol.*, **44,** 61.

Spray, C. M., and Widdowson, E. M. (1950). *Brit. J. Nutrit.*, **4,** 332.

Stearns, G., and McKinley, J. B. (1937). *J. Nutrit.*, **13,** 143.

Steinitz, F. (1904). *Jb. Kinderheilk.*, **59,** 447.

Streeter, G. L. (1920). *Contr. Embryol. Carneg. Instn.*, No. 55, **11,** 143. Publ. No. 274.

Thomas, K. (1911). *Arch. Anat. Physiol., Physiol. Abt.*, p. 9.

Toverud, K. U. (1935). *Acta paediatr.*, **17,** Suppl. 1, p. 136.

Venn, J. A. J., McCance, R. A., and Widdowson, E. M. (1947). *J. comp. Path.*, **57,** 314.

Widdowson, E. M. (1950). *Nature.* **166,** 626.

——, McCance, R. A., and Spray, C. M. (1950). *Clin. Sci.*, **16,** 113.

MYOSITIS FIBROSA GENERALISATA

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Myositis fibrosa generalisata is one of the rarest of the diseases of the muscular system. The number of authentic cases in the literature is small, and it is the purpose of this article to review the literature and to add a further case which has many features in common with those already described.

The onset of the disease is insidious. The patient usually complains of stiffness in one of the limbs, more often a lower limb. This stiffness is unaccompanied by pain but it is progressive and interferes with normal voluntary movement. Examination of the affected muscle reveals the presence of a small, painless, indurated area, which spreads until the whole muscle belly becomes involved. Similar areas appear in other muscles at a later date. All the affected muscles are firmer than normal. At first, the volume of the muscle remains unaltered, but later there is a marked diminution, with concomitant hardening of muscle texture. With the shortening of the muscle tendons, contractures develop and the patient becomes markedly deformed. There is progressive limitation of active and passive movements. In severe cases, the patient soon becomes bedridden.

As a rule, the facial muscles and sphincters are not involved. The masseter muscle is sometimes an exception and this interferes with movement of the jaw. The skin is never affected, a fact that distinguishes this disease from dermato-myositis.

In the initial stages there is an acute phase with rapid involvement of muscle groups, although little interference with general health is experienced. This stage is followed by periods of exacerbation and remission during which the patient may regain some muscle function. In some cases the whole course of the disease is more rapid.

Two features are important: there is neither fever nor pain.

The affected muscle responds to faradism but is hypotonic. Examination of the central nervous system shows no abnormality. Under anaesthesia the muscles retain their firm texture, and passive movement is limited by the degree of muscle contracture.

A definite diagnosis can be made only by microscopical examination of the muscle tissue. This shows hyaline degeneration, loss of cross striation and great variation in size of the muscle fibres. There is usually much increase of fibrous tissue, which surrounds and invades the involved muscle fibres. Round-cell infiltration may, or may not, be present.

Biochemical examination of affected muscle has shown a reduction in creatine content.

Treatment is, unfortunately, not satisfactory. No drug up to the present time has been found to be of any real value, although Blau (1938), recorded some relief from the use of glycocol. Physiotherapy and massage can be of benefit both from a psychological and a therapeutic aspect.

The prognosis is poor. In a later stage of the disease there is a progressive loss of weight and deterioration in well-being, and most of the patients die ultimately from intercurrent infection.

Review of the Literature

On a search of the literature, 11 authentic cases were observed: five patients contracted the disease in childhood and six in adult life. There are reports of a further five or six which can be regarded as atypical.

Onset during Infancy or Childhood. Janicke (1895) was the first author to describe the condition in detail. His patient was a three-year-old illegitimate girl. A small, firm nodule was felt in the left sternomastoid muscle. This nodule enlarged until the whole muscle belly became indurated. Subsequently, similar swellings appeared in other muscle bellies throughout the body. Three months after the onset of the disease all the affected muscles, with the exception of the pectoral group and the right biceps, had returned to almost normal consistence. Later, however, the right trapezius muscle again became indurated and this was followed by involvement of the right rectus abdominis muscle. Stab and streak cultures, prepared from muscle tissue fluid, were sterile. A biopsy specimen was taken from the right biceps, and it was noticed

that there was a pronounced grating of the knife as the specimen was cut. Janicke gave a masterly description of the microscopic appearances. There was marked variation in the size of the individual muscle fibres, normal breadth and cross striations were rare, and many of the fibres were grossly swollen. Between these fibres atrophied muscle elements were prominent. Janicke considered that these findings showed distinct degenerative changes in the muscle parenchyma. There was marked alteration in the interstitial tissue, individual muscle fibres being forced apart by proliferating broad bands of dense, connective tissue. True cellular infiltration was not seen and the vessel walls were normal.

Litchfield (1903) described a case of widespread interstitial myositis in a girl of 4 years. This patient exhibited many of the characteristic features of myositis fibrosa generalisata but, in view of a strong family history of syphilis, the author considered that syphilis was responsible for the pathological changes in the muscles.

Batten (1904) described a case in a girl, aged 9 months, whose symptoms developed with involvement of muscles of the lower limbs and back, followed by similar changes in the right sternomastoid muscle and in muscles of the upper limbs and abdomen. At the age of 6 years the child was in a rigidly flexed position with the head tilted towards the right. Examination of the affected muscle after death showed fibrous tissue infiltration between the individual muscle fibres, many of which were atrophied and showed fatty degeneration.

In 1930 Price recorded a case of a girl of $3\frac{1}{2}$ years, who reported with a hard, painless swelling in the right scapular region. This had fluctuated in size. Similar swellings appeared later in both sternomastoid muscles, the right brachialis and pectoralis major muscles. Biopsy from a pectoral muscle showed fibrous tissue, which had replaced and surrounded bundles of muscle fibres. There was no round-cell infiltration.

Schwab, Brindley, Bodansky, and Harris (1932) described a case of a Negro boy of 14 years, who reported with the history of a dull ache in the upper part of the chest wall, followed a few weeks later by stiffness and diminution in ability to use his hands. Similar symptoms appeared in the lower limbs. Eventually, almost all the muscles of the body were indurated, and the authors described the sensation, on palpation of these muscles, as not unlike a 'sand-bag.' The facial muscles were entirely unaffected with the exception of the masseter muscles, which were indurated. There was only slight involvement of the sternomastoid muscle. The strength of all the involved muscles was impaired. There was marked limitation of movement of upper and lower limbs. The boy was admitted to hospital at the age of 15 but died three months later with an infiltrative tuberculous lesion of the left lung. Biopsies of the muscle taken before death and tissue obtained at the post-mortem examination showed evidence of muscle degeneration, inflammation, and fibrous tissue proliferation. There was the usual variation in the size of individual muscle fibres, in many of which the striations had disappeared entirely: in other areas only longitudinal striations were present. Hyaline degeneration and hydropic infiltration were noticeable. There were varying numbers of inflammatory cells throughout the muscle tissue, some diffusely scattered, others arranged in collections around the more degenerated muscle fibres. Most of these cells were lymphocytes. Fibrous tissue of primitive type was present in varying amounts and occupied about 10% of the muscle volume. It is interesting to note that an examination of the myocardium showed a slight increase in the size of muscle fibres with granularity of the cytoplasm, an increase in fibrous tissue, and round-cell infiltration.

Blau (1938) placed a further case on record. A girl of 15 years complained of progressive limitation of movement in the joints of the limbs, accompanied by stiffness. Difficulty was experienced in using her hands and in walking upstairs. She was admitted to hospital at the age of 34 with atrophy of all skeletal muscles and generalized contractures limiting passive and active movements of the joints. The muscles were hard and inelastic. A biopsy from the left deltoid showed severe degenerative changes, fragmentation, and vacuolation of the individual muscle fibres. Cross striations were indistinct and occasional inflammatory cell infiltration was seen.

In 1941 Ellermann (1943) described a woman of 29 years, who had noticed a series of infiltrations in both thighs since childhood. Further swellings had appeared one year previously (1940), and the skin was found to be bound down to the deeper structures. There was no evidence of scleroderma. Biopsy was not convincing, but he considered, despite the very slight histological changes, that the condition was a true myositis fibrosa generalisata. This might be regarded more accurately as an atypical case.

We do not consider that the cases described by Schüller (1903) and Kagan (1936) fall into the category of this disease. A case described by Berghman (1874) is difficult to interpret but does not appear to resemble myositis fibrosa.

Onset in Adult Life. In 1923 Burton, Cowan, and Miller reviewed the literature and reported a total

of three cases in which the condition had begun in adults—namely those of Gies (1879), Kreiss (1886) and Gowers (1899). In a more recent review by Schwab *et al.* (1932), some doubt was expressed as to whether these cases should be included as typical of the disease. In the patients described by Gies (1879) and Kreiss (1886) only the lower limbs were affected: there were skin changes and the extent of involvement was very limited. The authors considered that the symptoms described in Gower's (1899) patient could be explained by a diagnosis of peripheral neuritis rather than of myositis fibrosa generalisata. The authors added an additional case, a woman who complained of stiffness of the arms and legs at the age of 22 years. Three years later she was bedridden and markedly deformed. A biopsy of the left gastrocnemius muscle showed the usual histological findings with round-cell infiltration and, in addition, evidence of chronic arteritis. This patient improved but recrudescence followed a miscarriage. The case was reviewed again in 1931.

Schwab *et al.*, in their review of the literature, found only four typical and about as many atypical cases. They include the case described by Hoover in 1924, which although apparently typical was not confirmed by biopsy. This patient lived for two years. They also state that Rosenstirn (1918) in his review of myositis ossificans progressiva found two further cases. They, however, consider them to be atypical.

Ornsteen (1935) described a case in a man of 42 years who suffered from severe muscle spasm, particularly when under a nervous strain, gradual stiffness in the back, and difficulty in walking. The abdominal muscles were also involved and no relaxation of these muscles was found during sleep. The diagnosis was supported by histological examination.

Blau (1938) reviewed the literature and reported a total of eight authentic cases. He added an additional two cases: one has already been described; the other occurred in a man of 20 years in whom there was rapid involvement of all the skeletal muscles including the masseter muscle. A biopsy of the left pectoralis major muscle showed the usual microscopical findings; cellular collections were present and irregular plaques of sclerotic fibrous connective tissue were seen in the sections examined.

Somers (1939) added a further case in a man of 53 years, who complained of stiffness in the lower extremities, spine, and abdominal wall. This case was proved by biopsy of the right quadriceps muscle.

Benedek (1944) reported a case resembling myasthenia but, from histological examination, it was considered to belong to the myositis fibrosa group.

Strong (1949) described a woman of 54 years, who had marked limitation of flexion and extension of the fingers in both hands. The forearm muscles were felt to be in spasm. Equinus and cavus deformity of the feet were notable features and obvious wasting of the calf muscles was present. A biopsy of the left flexor digitorum profundus showed muscle fibres to be thinner than normal with a definite diminution in cross striation. There was no evidence of fibrosis but some round-cell infiltration was seen. This case should also be regarded as an atypical example.

Case History

J.W., a boy, aged 11 years, was admitted in June, 1949.

The child was illegitimate and had been brought up by his mother, who was in very poor circumstances. So far as can be ascertained there was no family history of a similar condition. The patient was the second child of the family. Pregnancy, labour, and delivery were normal; and, at birth, no detectable abnormalities were present. At the age of 8 months he was seen at a neighbouring children's hospital as the mother had noticed that he was not using his left arm. He was otherwise perfectly normal and healthy and had never suffered from any febrile illness. Examination at that time showed a slight degree of atrophy of the left upper limb, together with limitation of supination. During the succeeding weeks this atrophy became more marked but all muscles were functioning normally. A Fairbank's splint was applied but the child did not report back for re-examination.

At the age of 5 years and 4 months the boy was admitted to the same hospital, having fractured his left femur as the result of a fall. The mother stated that the child had been late in sitting up, feeding, walking and talking. At that time it was noted that the left upper limb was atrophied and was used very little. He was also noticed to be mentally backward. Atrophy of the other limbs was not noted. The fractured femur united satisfactorily in good position but, according to the mother, the child had never walked since. A few years later he was certified as a mental defective and admitted to a home from which he was transferred to the Western General Hospital, Edinburgh. Unfortunately the mother was a very poor witness and it was not possible to obtain a more detailed history.

On admission, in June, 1949, the child appeared happy and contented. His intelligence was obviously well below normal, but this was difficult to assess as he had received little or no education. He was completely bedridden and unable to sit up or to feed himself. He was afebrile. He was extremely deformed, lying on his right side with his lower limbs flexed at all the joints. There was marked atrophy of all four limbs. The skin over the entire body was perfectly normal. Almost all the muscles of the upper and lower limbs were firm and

indurated, and the tendons of these muscles stood out as tight bands, limiting joint movement and producing severe contractures. Both feet were in a marked equinus position and it was possible to dorsiflex the feet only slightly (Fig. 1a, b, and c). Extension of the knee joints was limited to just beyond a right angle, flexion of these joints also being interfered with although to a lesser extent. Passive extension of both hip joints was limited to about 110°; flexion, however, could take place to a greater extent. The upper limbs were less severely involved. Abduction of the shoulder was possible to about 45° and there was about 20° movement of the elbow joint. There was ulnar deviation of both hands.

(*a*)

(*b*)

On palpation, the volume of the affected muscle was diminished; pain was not felt, although the child complained of discomfort on attempted extension of all joints beyond the ranges mentioned. These muscles had a curious, indurated feeling. Subcutaneous tissue moved freely over the surface of the muscle bellies. There was no involvement of the muscles of the face nor of the abdominal wall but those of the back felt firm and had the same texture as those of the limbs. All other systems were perfectly normal. It is necessary to emphasize that no abnormality was detected in the central nervous system. The child suffered from severe constipation with faecal impaction.

Special Investigations. The following laboratory and other investigations were made.

(*c*)

FIG. 1.

(*a*) On admission, showing deformities in the upper limbs.

(*b*) and (*c*) Comparison with normal child of same age.

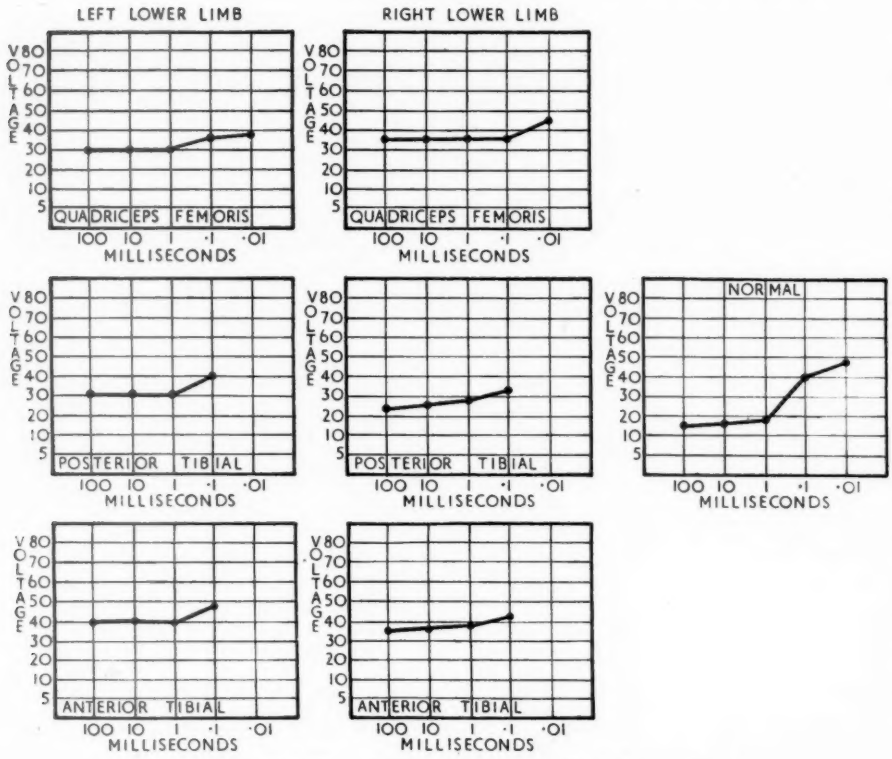

FIG. 2.—Electrical reactions of affected muscles.

BLOOD. The Wassermann reaction was negative, as also was the syphilis flocculation reaction.

Urea nitrogen was 16 mg. %; blood cholesterol 154 mg. %; serum calcium, 10·4 mg. %; serum alkaline phosphatase, 7 units (King); serum creatinine, 0·5 mg. %; serum inorganic phosphate (as P), 4·7 mg. %.

URINE. A 24-hour specimen (volume 390 ml.) gave total creatinine, 183 mg.; total creatine, 402 mg. (as creatinine).

MUSCLE REACTIONS. There was a poor response of affected muscles to faradism (Fig. 2). No R.D. present.

A radiograph of the skeleton showed general bony decalcification, and spindling of the shafts of the long bones. The right humerus showed cystic changes at the proximal extremity of the shafts. The pipe-stem appearance of the humeral shaft is readily seen in Fig. 3.

HISTOLOGY. Biopsy was carried out on two occasions, the tissue being obtained from the left sartorius, the right and left gastrocnemii, and the left triceps. In all cases there was marked resistance to the knife, almost amounting to a grating sensation, especially when the right gastrocnemius specimen was excised. The muscles were pale and firm in texture.

Biopsy material from the four muscles excised was examined. The pathological changes in all were of a similar type but differed in degree. They consisted of degeneration proceeding to disappearance of muscle fibres, and replacement by fibrous and fatty tissue.

The muscle fibres varied greatly in size and staining reaction. Some had undergone hyaline necrosis: they stained vividly with eosin, and had completely lost their cross-striation. Some of these hyaline fibres were much larger than normal; others were abnormally small. Other fibres stained faintly with eosin. Most of these showed unusually conspicuous longitudinal striation and had lost their cross-striation, but in a few fibres the transverse markings remained clear. These pale fibres also varied greatly in size. In the more severely affected muscles, there had been a great loss of muscle fibres: the bundles had been broken up, some being

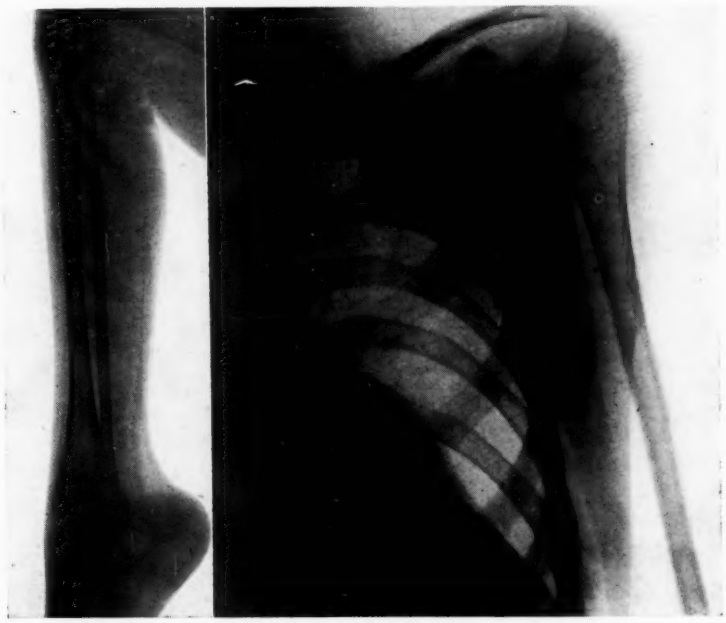

FIG. 3.—Radiographs showing 'pipe-stem' appearance of the shafts of long bones.

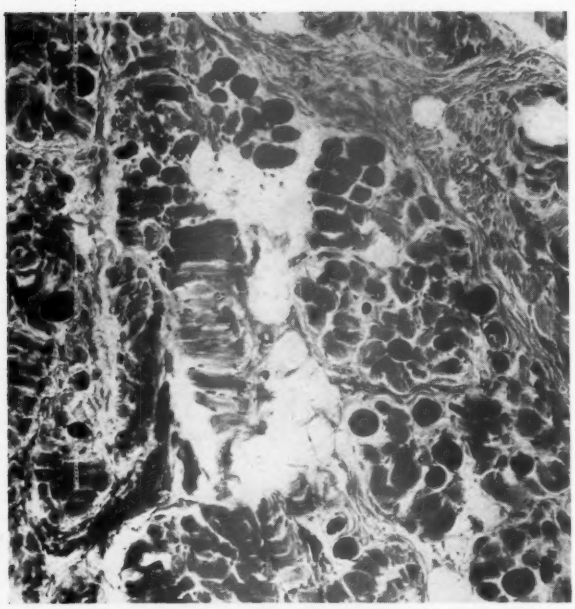

FIG. 4.—Photomicrograph of left gastrocnemius showing some loss of muscle fibres, hyaline necrosis and variation in size of muscle fibres, slight fibrosis and fatty infiltration (haematoxylin and eosin × 85).

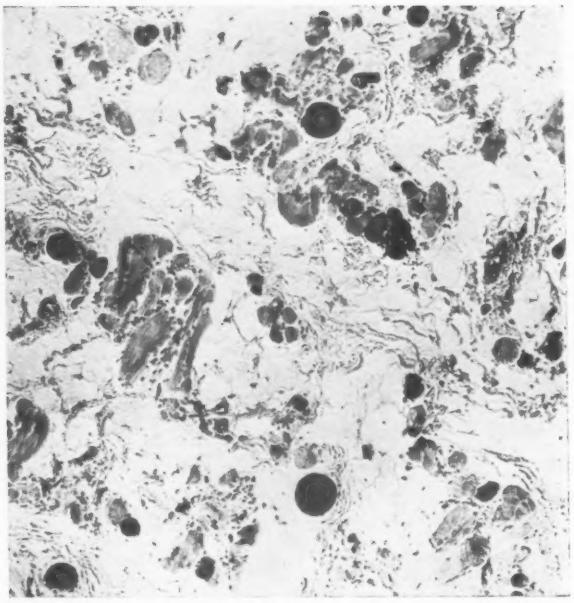

FIG. 5.—Photomicrograph of right gastrocnemius showing more advanced stage with great loss of muscle fibres, hyaline necrosis and variable size of muscle fibres. Replacement is mainly by fatty tissue (haematoxylin and eosin × 65).

represented by only a few, or even by single, muscle fibres (Fig. 5).

Replacement of the lost muscle fibres was partly by fibrous tissue, partly by fat. Fibrous replacement occurred by means of the development of fibrous tissue between the atrophied muscle fibres (Fig. 6) and, in addition, in some parts, collagen fibres appeared to have replaced some or all of the muscle fibrils within the sarcolemma sheath so that the outline of the replaced muscle fibres was retained. In some parts the atrophied muscle bundles, and even individual fibres within the bundle, were separated by loose connective and adipose tissue, without dense fibrosis.

FIG. 6.—Photomicrograph of triceps showing widely separated hyaline muscle fibres (some very large), dense fibrosis, and some fatty infiltration (azan × 65).

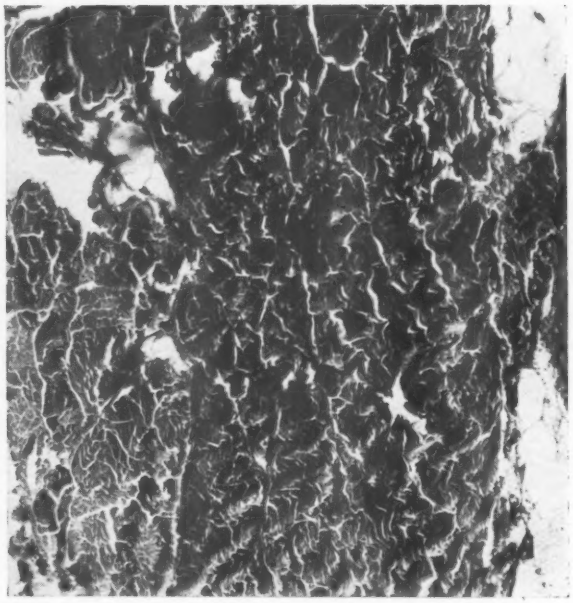

FIG. 7.—Photomicrograph of sartorius showing almost complete replacement of muscle by dense fibrous tissue and slight fatty infiltration (azan × 100).

The sarcolemma nuclei were unusually conspicuous, especially where fibrous replacement was in progress, and the new fibrous tissue contained many plump fibroblasts, but there was no lymphocytic or other inflammatory cell infiltration in any of the sections, except a collection of lymphocytes surrounding a small blood vessel in the muscle that was at the earliest stage of degeneration among those examined (left gastrocnemius).

The degeneration was most advanced in the sartorius muscle, where only traces of muscle remained, and replacement was partly by dense fibrous tissue and partly by fat (Fig. 7). In the left triceps the changes were identical except that they were not quite so far advanced. In both gastrocnemii, replacement was mostly by fatty tissue and there was no dense fibrosis. The process was considerably more advanced in the right than in the left gastrocnemius.

Active treatment was not adopted, as the process was considered to be so advanced that any orthopaedic procedures would be of little benefit. The child was discharged from hospital on July 25, 1949; his weight on discharge was 15·4 kg.

He was seen again on November 16, 1949, when it was found that all the affected muscles were much softer and the degree of movement of the joints of the upper limbs, especially the elbow joint, had increased. He was still unable to sit up and to feed himself but was using his fingers more freely. There was no further involvement of other muscle bellies.

Discussion

The essential features of myositis fibrosa generalisata have been clearly enumerated by Somers in 1939. These are the insidious onset, the progressive nature of the disease, the absence of facial and sphincter involvement, the afebrile course, the sand-bag feeling of the more severely involved muscles, and the typical histopathological findings.

We have been unfortunate in not obtaining a more detailed history from the mother especially as to whether the child had complained of stiffness of the limbs. To the best of our knowledge the course of the disease has been painless and unaccompanied by fever. The disease appears to have begun in the left arm and, between the age of 5 years and the time of admission, the other limbs have also become involved. There is no doubt that the texture of the muscle is similar to that found in typical cases of myositis fibrosa generalisata. On admission, the appearance of the child closely resembled that of the photograph of Batten's case in ' Diseases of Children ' (in Garrod, Batten, and Thursfield, 1949). In common with other reported cases there was no evidence of involvement of the central nervous system or of the skin. The electrical responses of the muscles showed no reaction of degeneration.

Typical degenerative changes were found in the muscle fibres. The amount of fibrous tissue replacement was less than has been reported in many other cases, and infiltration of the degenerated muscle by fatty tissue was more prominent. This feature is not referred to in previous case reports, but its presence is obvious in the illustration of the case reported by Burton, Cowan, and Miller (1923). Round-cell infiltration was almost completely absent. In this respect our case differed from the cases reported by Litchfield (1903), Burton *et al.* (1923), Schwab *et al.* (1932), Blau (1938), and Strong (1949), but resembled those reported by Janicke (1895), Batten (1904), Price (1930), and Ornsteen (1935).

The histological features were thus sufficiently distinctive to justify the inclusion of the case in the category of myositis fibrosa generalisata.

Further support for this diagnosis was provided by a study of the creatine metabolism, by means of which the extent of muscle degeneration can be judged. Children normally excrete creatine in the urine owing to their inability to store it. The creatine output, however, ceases about the age of puberty (Marples and Levine, 1936). Creatinine excretion in the urine increases during infancy and childhood. According to Behrendt (1949) a child of 11 years excretes about 2·7 mg. per kg. body weight of creatine and 20 mg. per kg. body weight of creatinine in 24 hours.

In our case the urinary creatine output was 402 mg. in 24 hours and of creatinine 183 mg. Our patient weighed about 15·4 kg. The normal daily creatine excretion for this child of 11 years should, therefore, be 41·6 mg. and that for creatinine should be 308 mg. It is thus evident that there is a gross excess of creatine excretion with a corresponding diminution in creatinine output. This indicates an extensive degree of muscle destruction and degeneration.

Schwab *et al.* (1932) found that creatinuria was a notable feature of the disease, more than 40% of the total creatine being excreted as creatine even with a meat-free diet. Biochemical analysis of the muscle specimen obtained from their patient showed an unusually low creatine content. Those muscles exhibiting microscopical evidence of marked inflammatory changes had the lowest creatine content, but this amount was reaching saturation point for the affected muscle. Treatment with glycocol in an attempt to restore creatine content of muscle is, therefore, unlikely to have much beneficial effect. It is important to realize that there is no skin involvement, distinguishing it clearly from dermatomyositis. This excludes cases described by Nixon (1907), Taussig (1932), and Cross (1934).

Little is known concerning the aetiology of

myositis fibrosa generalisata because of its infrequent occurrence. There does not appear to be any hereditary or familial diathesis. Batten (1904) considered that there might be some relationship to the more common condition of myositis ossificans progressiva, and this was considered not impossible by Schwab *et al.* (1932) who pointed out that ossification of muscle tissue was preceded by myositis in almost every case. However, to our knowledge, no case of myositis fibrosa generalisata has been found to progress to myositis ossificans. Jendrassik (1911), quoted by Blau (1938), considered the disease to be a special type of degenerative myopathy. Blau himself thought that it was probably related pathogenetically to the localized myositides.

There is considerable difference of opinion amongst authors regarding the inflammatory nature of the disease. Most authors regard round-cell infiltration as evidence of inflammation, but such infiltration has not been a constant feature in reported cases. The afebrile course of the illness provides no evidence of an infective origin, and the round-cell infiltration may well be a reaction to the presence of degenerating muscle fibres. It may be a transient phenomenon, present only at certain stages of the pathological process.

A comparison between myositis fibrosa generalisata and progressive muscular dystrophy reveals many similarities, although some authorities consider that there is little difficulty in distinguishing the two conditions. Macroscopically, in both diseases the muscles are pale and firm, differing only in degree. Microscopically, in both, the muscle fibres vary in size, some being larger and others smaller than normal. In both, they show hyaline and fatty degeneration, loss of cross striations, and ultimate disintegration. In progressive muscular dystrophy there is an increase in the number of sarcolemma nuclei. This feature has not been described in previous cases of myositis fibrosa progressiva, but it was present in our case. In progressive muscular dystrophy the replacement of the lost muscle fibres by fatty tissue is much more characteristic than in myositis fibrosa generalisata, but in the later stages fibrosis supervenes and produces a condition closely resembling that of myositis fibrosa. In our case, the combination of fatty infiltration of the less severely affected muscles, and fibrosis of those at a later stage of the disease, was a further point of resemblance to progressive muscular dystrophy. It is evident, therefore, that the pathological changes in the two diseases closely resemble one another, and differ in degree rather than in kind.

Radiological changes in the long bones in progressive muscular dystrophy were described by Epstein and Abramson (1941). These included symmetrical diminution in the size of the scapulae, a large humeral head in relation to a small, shallow glenoid fossa, and slender humeral shafts giving a 'pipe-stem' appearance. The latter radiological changes were present in our case.

We consider that our case, which most closely resembled myositis fibrosa generalisata in its principal clinical and pathological features, and yet had certain points of resemblance to progressive muscular dystrophy, may be regarded as providing some evidence to suggest that myositis fibrosa generalisata is one form of progressive muscular dystrophy, and is essentially a degenerative, and not an inflammatory, lesion of the muscles. This is in agreement with the opinion of Jendrassik (1911).

Summary

The symptomatology and pathology of recorded cases of myositis fibrosa generalisata is presented, and an additional case is described.

There is evidence to suggest that the disease is not a separate clinical and pathological entity, but one form of progressive muscular dystrophy.

We wish to thank Dr. A. B. Donald, Medical Superintendent of the Western General Hospital, Edinburgh, for referring this case; Mr. J. J. Mason Brown for permission to publish this article: and Miss C. Brydone, of the Department of Clinical Photography, Royal Hospital for Sick Children, Edinburgh, who took the photographs.

References

Batten, F. E. (1904). *Trans. clin. Soc. Lond.*, **37**, 12.
———. In Garrod, A. E., Batten, F. E., and Thursfield, H. (1949). 'Diseases of Children,' 4th ed., vol. 2, p. 273. London.
Behrendt, H. (1949). 'Diagnostic Tests for Infants and Children,' p. 173. New York.
Benedek, L. (1944). *Mschr. Psychiat. Neurol.*, **109**, 93.
Berghman, G. (1874). *Svenska LäkSällsk. Förh.*, p. 107. Abstr. *Zbl. Chir.* (1874), **1**, 618.
Blau, A. (1938). *J. Mt Sinai Hosp.*, **5**, 432.
Burton, J. A. G., Cowan, J., and Miller, H. (1923). *Quart. J. Med.*, **17**, 103.
Cross, A. G. (1934). *Lancet*, **2**, 1104.
Ellermann, M. (1943). *Acta psychiat. Kbh.*, **18**, 411.
Epstein, B. S., and Abramson, J. L. (1941). *Arch. Neurol. Psychiat., Chicago*, **46**, 868.
Gies, T. (1879). *Dtsch. Z. Chir.*, **11**, 161.
Gowers, W. R. (1899). *Brit. med. J.*, **1**, 65.
Hoover, C. F. (1924). Tice's 'Practice of Medicine,' Vol. 6, p. 543. Hagerstown, Maryland, U.S.A.
Janicke, O. (1895). *Dtsch. med. Wschr.* (Vereins-Beilage), **21**, 117.
Jendrassik, E. (1911). Cited by Blau, A. (1938).
Kagan, L. (1936). *Jb. Kinderheilk.*, **147**, 207.
Kreiss, A. (1886). *Berl. klin. Wschr.*, **23**, 877.
Litchfield, W. F. (1903). *Aust. med. Gaz.*, **22**, 516.

Marples, E., and Levine, S. Z. (1936). *Amer. J. Dis. Child.*, **51**, 30.
Nixon, J. A. (1907). *Lancet*, **1**, 79.
Ornsteen, A. M. (1935). *Ann. Surg.*, **101**,-237.
Price, I. I. (1930). *Brit. med. J.*, **1**, 1131.
Rosenstirn, J. (1918). *Ann. Surg.*, **48**, 485.
Schüller, A. (1903). *Jb. Kinderheilk.*, **58**, 193.
Schwab, E. H., Brindley, P., Bodansky, M. and Harris, T. H. (1932). *Ann. intern. Med.*, **6**, 422.
Somers, D. C. (1939). *J. Bone Jt Surg.*, **21**, 414.
Strong, J. A. (1949). *Ann. rheum. Dis.*, **8**, 158.
Taussig, L. (1932). *Arch. Derm. Syph., Chicago*, **25**, 882.

COOLEY'S ANAEMIA IN SINHALESE CHILDREN

BY

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Cooley's anaemia is a grave progressive anaemia occurring almost exclusively in children of Mediterranean stock. It is congenital and often familial (Cooley, 1949).

Racial Distribution

The first cases reported were all confined to those of Mediterranean stock, though Cooley denies a strictly racial incidence and believes that the mutation may occur in any race for some reason not yet discovered.

Nine cases have been reported from India, the last four being reported in the same paper by Chandra and Chaudhuri from Calcutta (1950). One case has been reported from China and three cases have been published occurring in Chinese of pure stock living in America (Foster, 1940; Gardner, 1947; Scott, 1947). Two cases in Negro children have been reported by Dameshek (1943) and Faber and Roth (1946).

This entity has now been identified in the Sinhalese, and is here reported for the first time from Ceylon. Chanmugam in his ' Anthropometry of the Sinhalese and Ceylon Tamils ' (1949), basing his conclusions on 29 measurements and 15 indices, says that the Sinhalese and Tamils are similar to the Mediterranean races. He suggests that the Sinhalese probably originated from Baluchistan, some settling at Minicoy, and the others on the west coast of Ceylon. The brachycephaly of the Sinhalese, he suggests, may have originated in the north of the Hindukush or southern Europe. The Sinhalese are of the same moderate stature as the Mediterranean race which, according to Coon (1939), occupied an unbroken zone from Spain across the Straits of Gibraltar to Morocco and eastward. Shanklin (1946) found two varieties of the Mediterranean race living in the Transjordan and Syrian deserts. The Basques, who are of the same stature as the Sinhalese and Tamils, speak a language which, according to Coon, may have been brought from western Asia. From these observations of Coon, Shanklin, and Chanmugam we may claim that the Sinhalese are of Mediterranean stock.

Cooley's anaemia falls into a group with a familial and racial entity distinct from the conglomeration of anaemias described by Von Jaksch. The appearance of these children is characteristic

FIG. 1.—Photographs of cases 1 and 2 (brothers). Note the great facial resemblance, the high cheek bones and the flat noses which are not racial characteristics of the Sinhalese. The children have mongoloid facies.

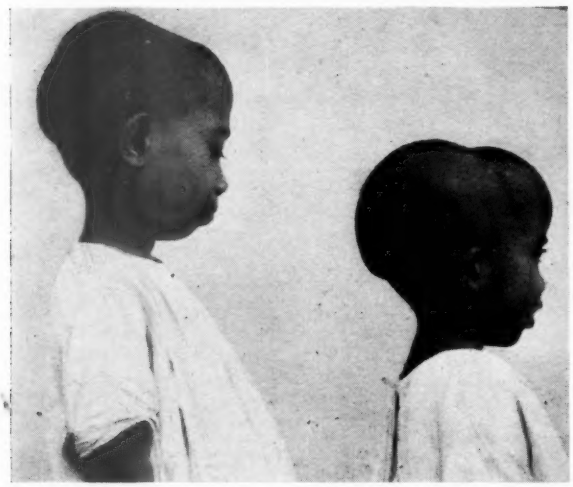

FIG. 2.—Photograph of cases 1 and 2 showing marked irregularity and bossing of skull.

(Figs. 1 and 2). They exhibit dwarfism to some degree and also mongoloid facies but these features are not always present. In any case they are not an early feature. The appearance of the skull is often characteristic in well developed cases. There is gross bossing giving the ' hot cross bun ' appearance, and enlargement of the malar bones. The anaemia is usually severe. There is pallor, which produces a muddy-yellow complexion, but no true jaundice. The spleen is greatly enlarged and firm. The liver is enlarged to a lesser extent. The blood shows a hypochromic anaemia which may be macrocytic or microcytic, but the volume index is low. The blood picture shows marked poikilocytosis, anisocytosis, polychromasia, excessive fragmentation, nucleated cells, basophilic stippling and target cells, and high normoblast and reticulocyte counts. The white cell count is also moderately increased. The myelogram reveals a very high erythroid reaction. There may be more than a reversal of the normal ratio of myeloid and erythroid cells (Figs. 3-6).

Case Histories

Case No. 1. E.D., a Sinhalese boy aged 7 years, weighing 27 lb., height 3 ft. 5½ in., was admitted to the Lady Ridgeway Hospital, Colombo, on May 5, 1950, with a history of enlargement and deformity of the head for two years.

The lumps on the head appeared first as small nodules over the frontal region of the skull, one on each side, followed by two others on the parietal regions, which later extended to the occipital. While in hospital this patient developed an irregular pyrexia which lasted for over two weeks.

Two years before the present complaint the patient had had oedema of the whole body with fever for one month.

Both parents are alive and healthy. The patient was the third of five children, having two brothers and two sisters. The elder sister was pale and anaemic and showed a ' lump ' over the posterior part of the skull. She had three normoblasts per 100 white blood corpuscles. The red cells were normal and did not show any anisocytosis, poikilocytosis, or target cells.

Blood films were made from 20 members of the family including parents, brothers and one sister, maternal aunts and uncles, maternal grandparents and several first cousins on both sides, but they revealed no abnormality except in the elder brother and sister.

On examination the patient was seen to be undernourished, pale, and anaemic. There was gross bossing of the skull. The bridge of the nose was depressed. The malar bones were prominent, the facies was mongoloid, the tongue was pale, moist, and clean. The pulse rate was 78 per minute; volume and tension were good.

The heart was within normal limits with normal sounds. The lungs were clear. The abdomen was distended but no free fluid was present. The spleen was enlarged to 6 in. below the costal margin with a smooth surface, firm consistency, and regular margin.

Blood analysis reports are set out in Table 1.

The x-ray appearances of the metacarpals and phalanges of the hand showed a mosaic pattern or lacing effect (Fig. 7). The transverse diameters of these bones

FIG. 7.—Phalanges and metacarpals show the lacing and widening effects and the irregular outline of the metacarpals.

were widened. These effects were present to a lesser degree in the metatarsals and phalanges of the foot. The bones of the skull showed an increase in width between the inner and outer tables, and the typical ' hair standing on end ' appearance (Figs. 8 and 9).

Case No. 2. L.D., the elder brother of case 1, 10½ years old, was admitted on June 5, 1950. His weight was 41 lb., and height 3 ft. 10 in. This boy was rather dull and had taken no interest in his surroundings since his second year. He had a poor appetite for food. He

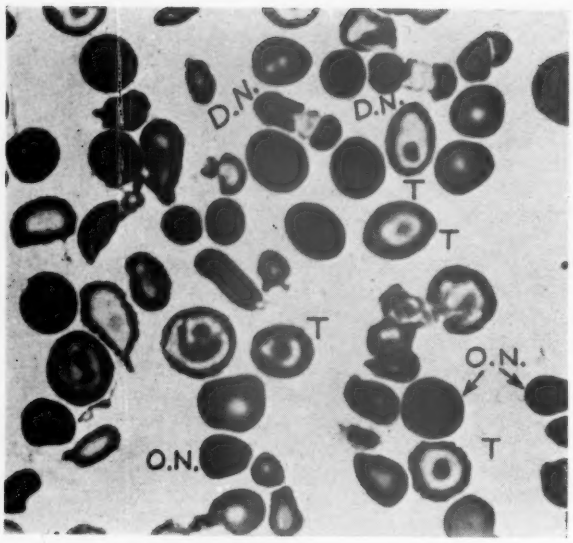

FIG. 3.

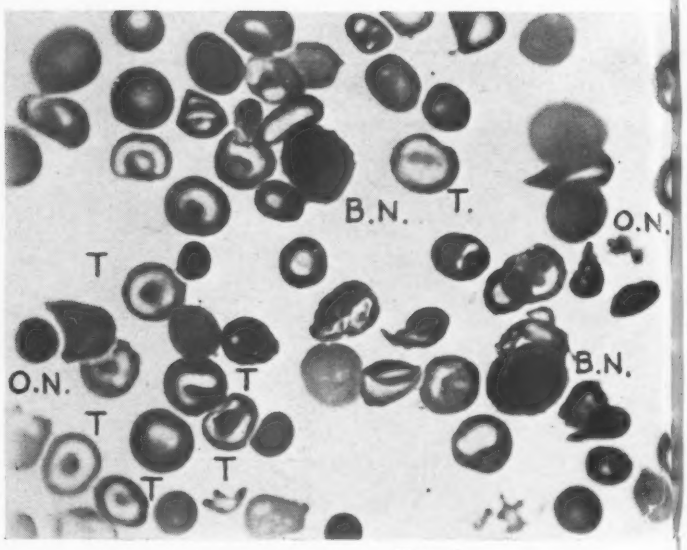

FIG. 4.

FIG. 3.—Blood film from case 1 (× 875) showing large number of target cells (T); ? dividing normoblast cells (D.N.); and orthochromic normoblasts (O.N.).

FIG. 4.—Blood film from case 3 (× 875) showing target cells (T); basophilic normoblasts (B.N.) orthochromic normoblasts (O.N.).

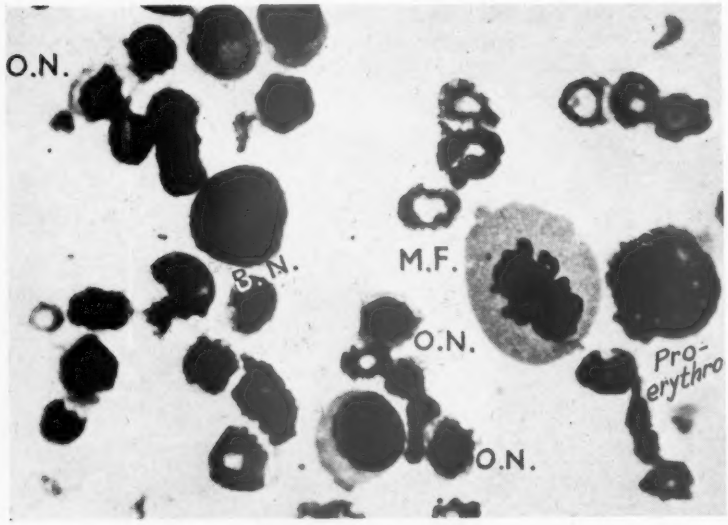

FIG. 5.

FIG. 5.—Film of marrow from case 1 (× 875). Mitotic figure (M.F.) is seen, also basophilic normoblast (B.N.) and orthochromic normoblasts (O.N.).

FIG. 6.—Marrow film from case 4 (× 875) showing mitotic figure (M.F.), pro-erythroblast and orthochromic normoblasts (O.N.).

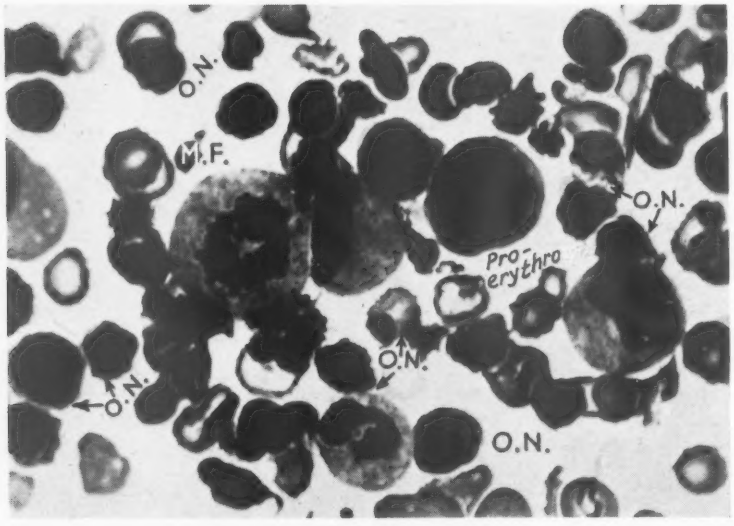

FIG. 6.

was constantly falling ill with attacks of cough, cold, and fever. In 1948 he was admitted for oedema of the feet to the Lady Ridgeway Hospital, Colombo, where he was under treatment for one month and went away partially relieved. He had a limp following a fall a year earlier.

His family history is described in case No. 1.

On examination the patient was seen to be pale, anaemic, and under-nourished. The malar bones were prominent. The facies was mongoloid. The feet were oedematous. The conjunctivae were pale. The tongue was pale, clean, and moist. The heart was within normal limits, with normal sounds. The lungs were clear. The abdomen was distended. The spleen was enlarged to the umbilicus, firm and not tender, with a smooth surface. The liver was enlarged to about 2 in. below the costal margin.

The x-ray appearances were similar to those of case 1, but less marked.

Blood findings are set out in Table 1.

FIG. 8 (Case 1).—Characteristic ' hair standing on end ' appearance over the frontal, parietal, and occipital regions. Mottled areas of rarefaction are also seen. Shadows of the cerebral vessels are clearly seen.

Case No. 3. S.A., a Sinhalese boy aged 3½ months, was admitted to the Lady Ridgeway Hospital on March 13, 1950, with a lump in the abdomen and anaemia of one month's duration and a high, swinging temperature which continued till death. The boy was in good health for one month after birth.

The patient was the youngest of five children. The parents were alive and healthy. The first three children were normal, but the fourth (boy) died of a similar complaint (a lump in the abdomen and anaemia) before he was a year old.

On examination the boy was apparently well nourished, weighing 10 lb. 12 oz. The skin was muddy-yellow. The heart and lungs showed nothing abnormal. The liver was enlarged to about 1½ in. below the costal margin. It was firm and not tender. The spleen was grossly enlarged extending to 1 in. above the left anterior-superior iliac spine. Nothing abnormal was discovered in the nervous system.

On radiography no bony changes were seen in the skull, metacarpals, or long bones. This child died during his fourth transfusion. No necropsy was allowed. The blood findings are set out in Table 1.

FIG. 9 (Case 2).—The ' hair standing on end ' appearance less well marked than in Fig. 8.

Case No. 4. D., a Sinhalese boy aged 1½ years, was admitted to the Lady Ridgeway Hospital on October 27, 1949, for a lump in the abdomen and intermittent fever of one year's duration.

The boy was normal and healthy till the onset of the present illness.

He was the only child of normal and healthy parents.

The patient was undernourished, weighing 13 lb. 4 oz. He had a mongoloid

facies and a 'hot cross bun' appearance of the skull. The skin was a muddy-yellow.

The heart and lungs showed no abnormality. The liver was not palpable below the costal margin. The spleen was enlarged down to the umbilicus. It was firm and not tender; the surface was smooth. The spleen varied a great deal in size during the time the child was in hospital. The inguinal, axillary, and cervical glands were enlarged and shotty.

Radiographs showed that the parietal bones had the 'hair standing on end' appearance very slightly; otherwise the skull and metacarpal bones showed no abnormality.

The blood picture is seen in Table 1.

The child died during the fifth transfusion. No necropsy was allowed.

Discussion

We present four cases of Cooley's anaemia which were investigated. In addition there was a fifth case which could not be investigated fully as the parents refused admission to the hospital, although this patient showed the highest normoblast count of all in the peripheral blood (388 normoblasts per 100 W.B.C.s.). The spleen was grossly enlarged and he had the typical muddy-yellow complexion.

The bony changes shown in the radiographs of the metacarpal bones and the skull are present in the cases which belong to an older age group or have suffered from the condition for some time. The youngest patient, aged 3½ months, showed no

TABLE 1

BLOOD FINDINGS IN CASES 1-4.

Case No.	1	2	3	4
Red blood corpuscles (c.mm.)	3,630,000	1,820,000	1,540,000	2,200,000
White blood corpuscles (c.mm.)	30,200	10,400	21,200	8,800
Platelets (c.mm.)	210,000	230,000	—	102,000
Reticulocytes (%)	2·2	2·4	6·8	—
Differential count (%):				
Polymorphs	45	59	16	51
Lymphocytes	55	36	78	45
Eosinophils	0	5	2	0
Monocytes	0	0	0	4
Normoblasts (per 100 W.B.C.s)	24	19	92	21
Average size of red cells (μ) (Pijpers)	7·5	7·9	7·8	7·5
Corpuscular volume (ml./100 ml.)	34·7	22·0	—	27·9
Mean corpuscle volume	96·3	118·0		99·6
Mean corpuscle haemoglobin	31	31	— — —	34·2
Mean corpuscle haemoglobin concentration	36	25	— — —	34·4
Haemoglobin (g. Sahli)	8·8	5·6	6·4	6·12
Examination for malarial parasites on several occasions	nil	nil	nil	nil
Blood picture:				
Anisocytosis	+	+	+	+
Poikilocytosis	+++	+++	++	++
Erythroblasts	+++	+++	+++	+++
Basophilic stippling	+	+	+	+
Target cells	+	+	+	+
Fragility began at % NaCl	0·28	0·28	0·22	0·41
completed at % NaCl	0·12	0·08	0·16	0·38
Icteric index	7·0	— — —	8·0	6·0
Van den bergh Test Direct	—	—	—	—
Indirect	—	+ (faintly)	+ (faintly)	+ (faintly)
Bone Marrow (%):				
Myelocytes	4	10	2	— —
Eosinophilmyelocytes	0	0	2	— —
Metamyelocytes	1	4	0	— —
Polymorphs	6	8	2	— —
Eosinophils	1	2	2	— —
Lymphocytes	1	3	1	— —
Pro-erythroblasts	1	3	5	— —
Normoblasts (basophilic)	1	18	3	— —
,, (polychromatophilic and orthochromic)	85	52	82	— —
Mitotic figures	0	0	1	— —
Kahn and C.L.	— —	— —	— —	— —
Urine:				
Bile pigments and salts	nil	nil	nil	nil
Urobilin	1/40	nil	nil	1/10

radiological signs of the disease process, but the typical blood changes were present. The splenomegaly in this case was noticed by the parents at the age of 1 month.

Once the diagnosis has been made the disease is slowly progressive. The younger the patient, the more rapid the progress, and the shorter therefore the period of survival. Growth is clearly retarded, as was shown in our cases 1 and 2, which we consider below average in height and weight. The peculiar mongoloid facies is probably due to marrow hyperplasia in the maxillary bones producing the high cheek-boned appearance. There is no slanting of the eyes or inner canthus present as in true mongoloid idiocy, though some writers claim that these are present in their cases (Cooley, 1949). The bossing of the skull, which produces the ' hot cross bun ' effect or the grotesque lumps on the frontal and parietal or occipital regions, is due to the same reasons. In Fig. 2 the photographs of cases 1 and 2 show a striking facial resemblance. This is present even in the unrelated patients. The peculiar skin colour is apparent even in the dark brown skin of the Sinhalese, which takes on a muddy-yellow tint and is quite different from the colour produced by any type of jaundice.

The most striking change in the peripheral blood is the great preponderance of nucleated red cells, especially mature and partly mature normoblasts. In addition there are large numbers of target cells and abnormal forms, shapes, and sizes of red cells. The enlarged spleen is usually the earliest sign. The changes in it are probably due to its function of breaking down and disposing of the end-products of the fragmented cells. Whipple (quoted by Cooley, 1922) suggests that the storage in the liver of the haemoglobin-forming substances, which the marrow is unable to use, accounts for the hepatic enlargement. Cooley is of the opinion that the bony changes are an indication of a primary progressive abnormality of the marrow, or hyperplasia, due to long continued over-stimulation, and the bony striae are the result of irritation.

Polychromasia and a high reticulocyte count were present in our cases. The urobilin in the urine was within normal limits and the icterus index and indirect Van den Bergh reaction were very slightly raised. Cooley believes that the excessive fragmentation and peculiar irregular deposition of haemoglobin in the cells are related to one another and indicative of abnormalities in the physico-chemical structure of the cells, which causes them to go to pieces rapidly in the circulation. The destruction by fragmentation is more extreme than in any other anaemia, and might well be the reason for the great marrow stimulation and hyperplasia. The presence of numerous target cells is very striking. These cells are not peculiar to any one anaemia. They are present in sickle cell anaemia and anaemias due to liver disease. We have also seen target cells in abundance in blood films from cases of severe hookworm anaemia. It is probably a result and not a cause of the disease process. Punctate basophilia is a prominent feature and is probably due to a defect in the structure of the corpuscle. The red cell fragility to solutions of saline is reduced in this condition, in contradistinction to the increased blood fragility in haemolytic icterus, but we did not always find the widened span.

Marrow. The marrow showed a wide variety of cells with a marked preponderance of the erythroid series, especially of the normoblasts, which ranged from 70% to 85% of the cells. Most of the normoblasts were polychromatophilic or orthochromic and not basophilic. The pro-erythroblasts were few in number and the others were of normal range. There were in addition quite a number of mitotic figures with fascinating shapes and sizes of nuclei. Target cells were also seen but were probably from the peripheral blood.

X-ray Findings. All the bones reflected the extreme marrow hyperplasia. In our cases the shafts of the long bones showed widening of the marrow cavity and marked trabeculation along their length. There was thinning of the cortex in parts. The trabeculation was best seen in the carpus and the phalanges, producing a beautiful picture of the mosaic pattern. Spontaneous fractures are said to occur in these bones but our cases showed no such evidence. The appearance of the skull is quite characteristic in cases of some duration. The bones of the vault are thickened and bossed, and later the striking ' hair standing on end ' appearance or the ' golliwog ' skull. This is due to a hyperplasia of marrow between the inner and outer tables of the skull. These changes are also seen in sickle-cell anaemia but the thinning of the cortices is not so noticeable.

Wintrobe (1946) refers to a minor form of this condition which he terms thalassaemia minor in contradistinction to thalassaemia major which is the classical form of the disease. The former, he states, is present in the blood relations, parents and other siblings, of the patient. We examined 20 blood films from near relatives and only in one sister did we find any deviation from the normal. There was no irregularity of the haemoglobin distribution and there were no target cells, poikilocytosis, or polychromasia. Chini and Malaguzzi Valeri (1949) claim that there is a decreased fragility to hypotonic salines in thalassaemia minor. We have not been able to investigate this.

Nittis and Spiliopulos (1937) have suggested that this condition may be a peculiar form of malaria. None of our patients ever showed any malarial parasites in the blood. Their temperature charts were quite different to those of any type of malarial fever, but they were not given any anti-malarial remedies. Caminopetros (1938) claimed on the other hand that infecting his patients with malaria produced good results.

Summary

Four cases of Cooley's anaemia are reported from Ceylon in male Sinhalese children.

The two older patients showed marked radiological changes in the skull, long bones, and metacarpals and phalanges. The blood changes were typical.

Our thanks and acknowledgments are due to Dr. G. H. Cooray of the Department of Pathology, University of Ceylon, to Drs. Welikale and Jayamanne, of the X-ray Department of the General Hospital, Colombo, and to Messrs. G. Webster, Justin de Silva, A. S. Mahawatte and Vernon Jayawardena for technical help in preparing blood and marrow films and the photographs.

REFERENCES

Caminopetros, J. (1938). *Ann. Méd.*, **43**, 27.
Chandra, N. K., and Chaudhuri, K. C. (1950). *Indian J. Paediatr.*, **18**, 89.
Chanmugam (1949). *Ceylon Journal of Science* (section C), 4, Part 1, 1-18.
Chini, V., and Valeri, C. Malaguzzi (1949). *Blood*, **4**, 989.
Cooley, T. B. (1949). In Brennemann's 'Practice of Pediatrics,' vol. 3, ch. 16, pp. 54-66.
Coon, C. S. (1939). Quoted by Chanmugam. 'The Races of Mankind'. Pp. 39, 246, 293, 401, 404, 418, 431, 502.
Dameshek, W. (1943). *Amer. J. med. Sci.*, Hagerstown, Maryland, U.S.A., **205**, 643.
Faber, H. K., and Roth, B. M. (1946). *J. Pediat.*, **28**, 610.
Foster, L. P. (1940). *Amer. J. Dis. Child.*, **59**, 828.
Gardner, L. B. (1947). *J. Pediat.*, **31**, 347.
Jaksch, R. von (1889). *Wein klin Wschr.*, **2**, 435, 456.
Nittis, S., and Spiliopulos, G. (1937). *Amer. J. Dis. Child.*, **54**, 60.
Scott, A. V. (1947). *Chin. med. J.*, **65**, 77.
Shanklin, W. M. (1946). *Amer. J. phys. Anthrop.*, n.s., **4**, 323.
Wintrobe, M. M. (1946). 'Clinical Hematology,' 2nd edit., pp. 564-574. London.
Whipple, G. H. Quoted by Cooley, T. B. (1922). *Arch. intern. Med.*, **29**, 711.

COOLEY'S ANAEMIA IN A MALTESE CHILD

BY

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(RECEIVED FOR PUBLICATION DECEMBER 19, 1950)

Although almost all the earliest work upon this anaemia was done by Cooley (1927 and 1928), by Cooley and Lee (1925 and 1929), and by Cooley, Witwer, and Lee (1927) in America it soon became clear that the syndrome occurred often in the Mediterranean races. Indeed Davison and Wechsler (1939) believed that the disease originated in Greece, and had been spread to other countries by the conquering armies of Alexander the Great. The first case reported from Italy was by Ravenna and Canella in 1934. In recent years, however, examples have been reported in many other parts of the world. Fawdry (1944) has found 20 cases in Cyprus; Saracoglu (1943) reports four cases amongst Turks; one case is described in a Spanish child, by Sendrail, Lyon, and Lasserre (1936), and another in an English child by Bywaters (1938). Two have been found in Egyptian children (Diwani, 1944), two in Bucharan Jews (Schieber, 1945), and one in a South African of European descent (Altmann, 1946). Additionally, several cases have been reported in Hindus (Malhotra and Chuttani, 1944; Mukherji, 1938; Napier, Shorten, and Das Gupta, 1939); two in Brahmins (Patel and Bhende, 1939; Dhayagude, 1944); five in Chinese (Foster, 1940; Wang and Khoo, 1940); and two in Negroes (Stiles, Manlove, and Dangerfield, 1946; Faber and Roth, 1946). It is interesting to record that one of the Chinese mentioned by Wang and Khoo, and the negro mentioned by Stiles and his colleagues were, in each case, of remote Italian ancestry.

In spite of the close proximity of Malta to the Italian peninsula, the case described here is, as far as is known, the first example of the disease to have been reported from Malta.

Case Report

The affected individual is the sixth child of a family of seven. Two of his sisters had previously died from a severe anaemia, and the remaining four siblings are quite healthy. The family itself is of pure Maltese ancestry.

The patient was a boy aged 2 years. His mother stated that he was unduly pale at birth, in spite of a normal and speedy confinement. Ever since, he had been lethargic, weak, and mentally retarded. When 3 months old, the enlarged spleen was noticed by his parents, and this gradually increased in size. The subsequent story is that of a relentless, progressive pallor and weakness. Enuresis and a chronic cough latterly became troublesome.

On examination the child was seen to be muddy-complexioned, pale, and irritable. His head was large, and the frontal and malar bones prominent. His eyes were deep set and the nose was short and depressed. The abdomen was protuberant, and the firm hard spleen reached down to the umbilicus. The liver was palpable two inches below the costal margin. The heart was not enlarged clinically, but a soft, systolic, apical murmur was occasionally present. Scattered rhonchi were present in the chest. The central nervous system was normal.

Haematological data obtained in May, 1948, were as follows:

R.B.C.s 3,770,000 per c.mm.; Hb 52%; colour index 0·69; W.B.C.s 14,700 per c.mm.; platelets 220,000 per c.mm.

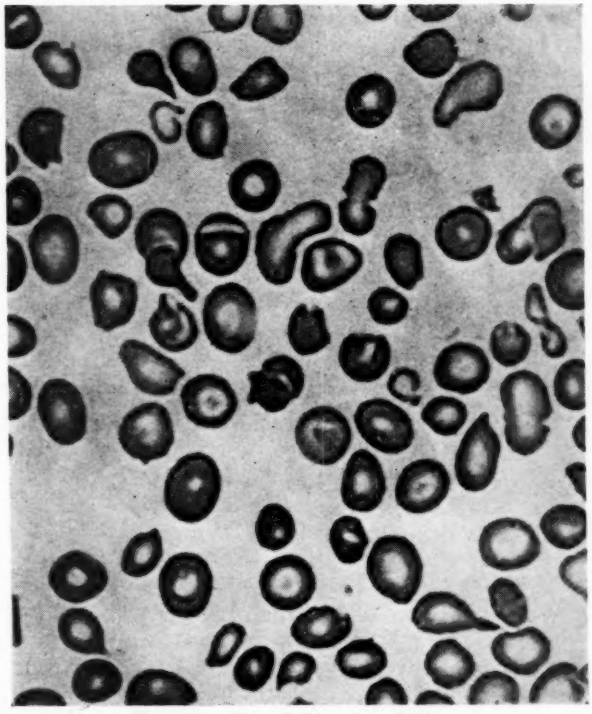

FIG. 1.—Blood film (× 800).

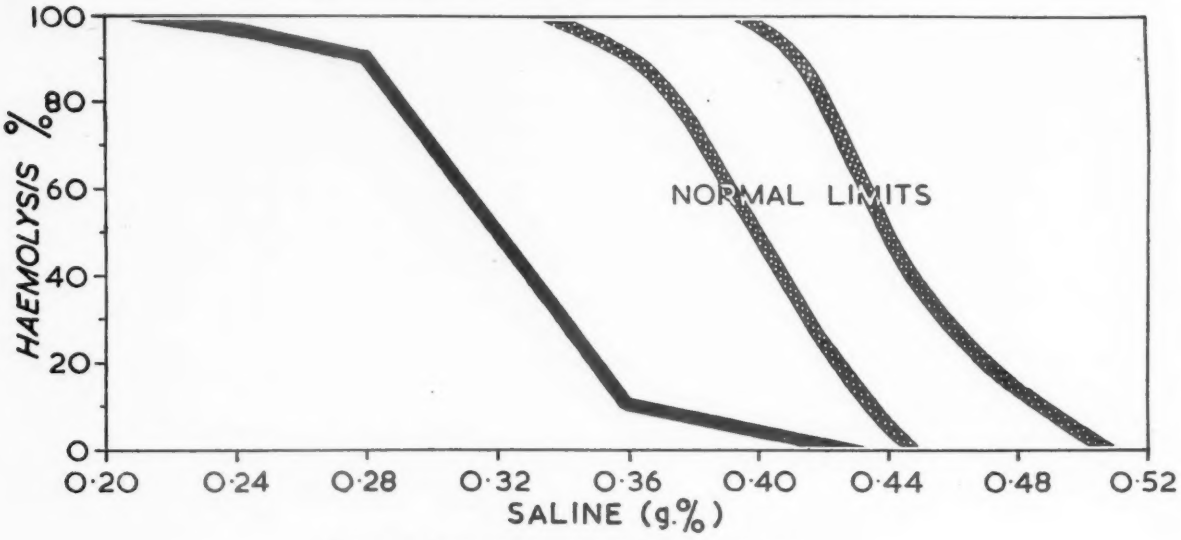

FIG. 2.—Curve of the differential fragility test.

The differential white cell count gave polymorphs 65%, lymphocytes 23%, monocytes 7%, eosinophils 1%, basophils 0%, normoblasts 4%.

Aniso- and poikilocytosis were marked (Fig. 1). Leptocytes were numerous and there were a few target cells.

A few thin 'hoop-type' cells with a pale rim of haemoglobin and a large central achromic area were present. No parasites were seen.

The erythrocytic indices were as follows: packed cell volume, 27·0; mean cell volume, 71·7 cμ.; mean cell diameter 7·2 μ.; mean cell thickness, 1·79 μ.; mean corpuscular haemoglobin concentration, 27·7%; diameter/thickness ratio, 4·0:1; standard deviation in size, 1·05 μ.

There were 200,000 reticulocytes per c.mm. (5·4%), and 15,000 stipple cells per c.mm.

The serum bilirubin level was 2 mg. %, Brucella agglutinations were negative (1/25 to 1/2,500). Schumm's test was strongly positive (+++), and Napier's test for kala-azar was negative.

Urine analysis gave urobilinogen +.

The differential fragility test showed a marked increase in saline resistance (Fig. 2).

The total fat in the faeces were 22%, and unsplit fat was 26% of the total fat.

Because the child did not cooperate no satisfactory pictures of the skull were obtained. Fig. 3 shows a typical increase in width of the metacarpal bones, with a thinning of the cortex.

In spite of intensive iron, vitamin, and liver therapy, no appreciative improvement was effected and the count when I last saw the child in October, 1948, was:

R.B.C.s, 3,190,000 per c.mm.; Hb, 46%; colour index, 0·69; W.B.C.s, 17,200 per c.mm.; reticulocytes, 6·8%.

The differential white cell count gave polymorphs 69%, lymphocytes 18%, monocytes 4%, eosinophils 3%, normoblasts 6%.

Aniso- and poikilocytosis were marked, and there were numerous leptocytes and target cells.

Differential Diagnosis. Syphilis was excluded by the Kahn reaction, and chronic malaria by the absence of parasites from numerous thick and thin blood films. Haemolytic anaemias, such as acholuric jaundice and sickle-cell anaemia, could be eliminated by the results of the fragility test, mean cell thickness, and absence of sickling in sealed preparations of blood after seven days' incubation at 37° C.

Leishmaniasis was unlikely in view of the absence of any fever, the presence of leucocytosis, a negative formol-gel test, and the absence of Leishman-Donovan

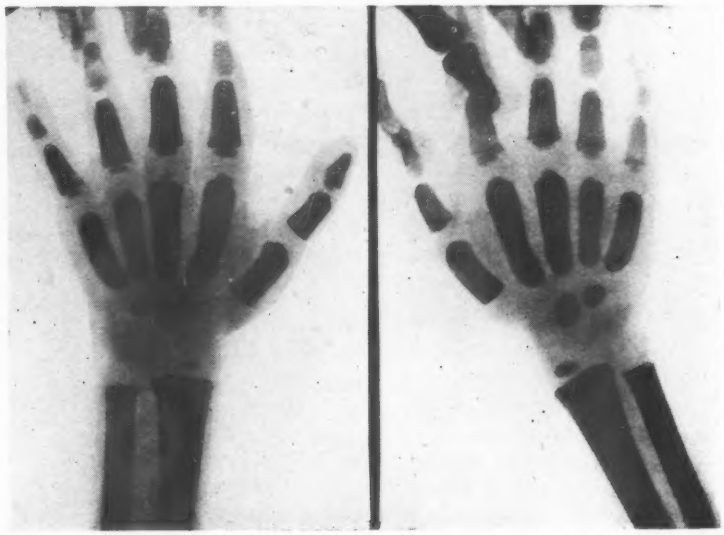

FIG. 3.—Radiograph of fore-arm and hand (E. B.).

bodies in the blood. Additionally, the time of onset was unusually early for kala-azar.

Primary bone diseases were excluded by x-ray evidence, and coeliac disease by faecal fat estimation. Nutritional anaemia was unlikely in view of a negative response to vitamins, iron, and liver therapy.

Points in favour of the diagnosis of Cooley's anaemia were the absence of response to treatment, the erythrocytic resistance to saline and cell thinness, the presence of target and stipple cells, a mongoloid facies, the history of other deaths in the family from an anaemia of childhood, and the skeletal changes demonstrated by radiography, and the typical spread of the Price-Jones curve (Fig. 4).

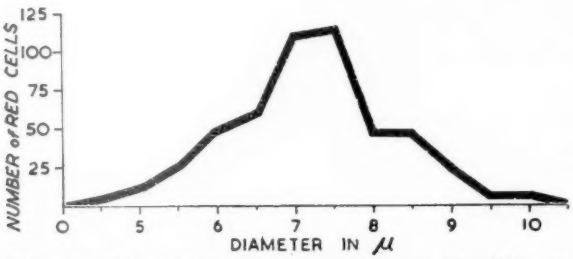

FIG. 4.—Price-Jones Curve (method of Humble and Belyavin, 1948).

Discussion

Two factors emerge from an analysis of these findings. First, the pallor which persisted from birth, and the appearance of a palpable spleen when 3 months old, indicates that the child was probably born a clinical example of the disease. Secondly, the presence of a considerable amount of methaemalbumen in the plasma, as indicated by a positive Schumm's haemochromogen test, is of significance from a haemolytic point of view. According to Fairley (1941) this pigment is formed from extracorpuscular haemoglobin when the blood is destroyed in large amounts, and its presence indicates the occurrence of an intravascular type of haemolysis. In this connexion, the similarity in the distribution of iron-positive pigment in Cooley's anaemia and in haemochromatosis is recalled (Sheldon, 1935; Nachtnebel, 1933). In both diseases heavy deposits are found in the liver, pancreas, stomach, salivary glands, suprarenals, upper abdominal lymph nodes, and skin; conversely, very little is to be seen in either the spleen or kidneys. Also, the pigment in the liver chiefly occupies the liver cells in the peripheral half of the lobule in both conditions, whereas the Küppfer cells are strikingly empty. In Cooley's anaemia the source of this pigment almost certainly appears to be a direct result of the increased intravascular haemolysis demonstrated by Schumm's test. In haemochromatosis, however, this explanation will not suffice, for, as Sprunt (1911) has pointed out, there is no evidence of increased blood destruction in this disease. Nevertheless, the similarity of the pigment distribution in the two cases raises the speculation as to whether the iron circulating in the blood is in a closely allied or identical form in both conditions, thus accounting for the almost identical absorption by the various organs and the characteristic muddy complexions found in the two diseases (Mills, 1938).

In familial acholuric jaundice, on the other hand, Schumm's test is invariably negative (Bingold, 1930). Furthermore, the pigment distribution is entirely different, and although iron-positive material may be found in the heart, thyroid, and gastric musosa in long-standing cases, the greatest accumulation occurs in the spleen and, to a lesser extent, in the Küppfer cells of the liver (Whipple and Bradford, 1932). This disparity in the quantity of splenic pigment found in these two familial, haemolytic anaemias can be at least partially rationalized by a consideration of the physiological action of the spleen upon the morphology of erythrocytes. Singer, Miller, and Dameshek (1941), working with dogs and guinea-pigs, noted that, after either ligation of the splenic vein or splenectomy, target cells appeared in the peripheral blood. Whitby and Hynes (1935) recorded not only the appearance of target cells following splenectomy, but also an increased erythrocytic resistance to saline. As Haden and Evans (1937) have shown that increased saline resistance indicates a diminution in mean cell thickness, and Barrett (1938) that target cells are less fragile than normal, the overall effect of splenectomy on erythrocytes would appear to be a diminution in the mean cell thickness. This is supported by the observation of Bradford and Dye (1936), who recorded a reduction in M.C.T. from 2·00μ to 1·81μ in one of their cases of Cooley's anaemia after removal of the spleen. Conversely, from the accumulated evidence it would appear that under the normal conditions of stasis in the spleen (Ham and Castle, 1940; Knisely, 1936a and b) the erythrocytes undergo an increase in thickness. It is logical, therefore, to presume that cells which are spherocytic, as in acholuric jaundice, will more readily succumb to these static conditions, rupture, and be destroyed *in situ*. On the other hand the leptocytic cells of Cooley's anaemia will be better equipped to withstand passage through this organ, and will emerge relatively unscathed. For this reason, therefore, it is possible to understand why removal of the spleen in acholuric jaundice effects such a considerable clinical improvement, although the tendency towards spherocytosis is only slightly ameliorated (Hawksley and Bailey, 1934; Hawksley,

1936). Similarly, as there is no pathological evidence of increased splenic haemolysis in Cooley's anaemia, removal creates no lasting improvement.

In conclusion, therefore, it would appear that the mechanism of cell destruction in these two familial haemolytic anaemias is quite different. In acholuric jaundice distribution of pigment and the effects of splenectomy indicate that the spleen is the site of the greatest erythrocytic destruction. In Cooley's anaemia, on the other hand, the absence of an excessive amount of iron in the spleen and the presence of methaemalbumen in the plasma indicates that haemolysis must be largely, if not entirely, intravascular.

Summary

Cooley's anaemia in a Maltese child is described. The presence of methaemalbumen in the plasma is recorded, and its significance discussed.

I wish to express my gratitude to the Deputy Director of Pathology, M.E.L.F., for permission to submit this paper.

References

Altmann, A. (1946). *S. Afr. med. J.*, **20**, 476.
Barrett, A. M. (1938). *J. Path. Bact.*, **46**, 603.
Bingold, K. (1930). *Folia haemat., Lpz.*, **42**, 192.
Bradford, W. L., and Dye, J. (1936). *J. Pediat.*, **9**, 312.
Bywaters, E. C. L. (1938). *Archives of Disease in Childhood*, **13**, 173.
Cooley, T. B. (1927). *Amer. J. Dis. Child.*, **33**, 786.
—— (1928). *Ibid.*, **36**, 1257.
——, and Lee, P. (1925). *Ibid.*, **30**, 447.
——, —— (1929). *Ibid.*, **38**, 103.
——, Witwer, E. R., and Lee, P. (1927). *Ibid.*, **34**, 347.
Davison, C., and Wechsler, I. S. (1939). *Ibid.*, **58**, 362.
Dhayagude, R. G. (1944). *Ibid.*, **67**, 290.
Diwani, M. (1944). *Archives of Disease in Childhood*, **19**, 163.
Faber, H. K., and Roth, B. M. (1946). *J. Pediat.*, **28**, 610.
Fairley, N. H. (1941). *Quart. J. Med.*, **10**, 95.
Fawdry, A. L. (1944). *Lancet*, **1**, 171.
Foster, L. P. (1940). *Amer. J. Dis. Child.*, **59**, 828.
Haden, R. L., and Evans, F. D. (1937). *Arch. intern. Med.*, **60**, 133-142.
Ham, T. H., and Castle, W. B. (1940). *Proc. Amer. phil. Soc.*, **82**, 411.
Hawksley, J. C. (1936). *J. Path. Bact.*, **43**, 565.
—— and Bailey, U. M. (1944). *Lancet*, **2**, 1329.
Humble, J. G., and Belyavin, G. (1948). *J. clin. Path.*, **1**, 77.
Knisely, M. H. (1936a). *Anat. Rec.*, **65**, 23.
—— (1936b). *Ibid.*, **65**, 131.
Malhotra, R. P., and Chuttani, P. N. (1944). *Indian med. Gaz.*, **79**, 198.
Mills, E. S. (1938). *Arch. intern. Med.*, **62**, 1004.
Mukherji, M. (1938). *Indian J. Pediat.*, **5**, 1.
Nachtnebel, E. (1933). *Amer. J. Path.*, **9**, 261.
Napier, L. E., Shorten, J. A., and Das Gupta, C. R. (1939). *Indian med. Gaz.*, **74**, 660.
Patel, N. D., and Bhende, Y. M. (1939). *Indian J. Pediat.*, **6**, 217.
Ravenna, F., and Canella, C. (1934). *Policlinico (prat.)*, **41**, 807.
Saracoglu, K. (1943). *Wien. med. Wschr.*, **93**, 217.
Schieber, C. (1945). *Lancet*, **2**, 851.
Sendrail, M., Lyon, A., and Lasserre, J. (1936). *Bull. Soc. méd. Hôp. Paris*, **52**, 902.
Sheldon, J. H. (1935). 'Haemochromatosis.' London.
Singer, K., Miller, E. B., and Dameshek, W. (1941). *Amer. J. med. Sci.*, **202**, 171.
Sprunt, T. P. (1911). *Arch. intern. Med.*, **8**, 75.
Stiles, M. H., Manlove, C. H., and Dangerfield, C. D. (1946). *Northw. Med., Seattle*, **45**, 23.
Wang, C. Y., and Khoo, F. Y. (1940). *Chin. med. J.*, **58**, 177.
Whipple, G. H., and Bradford, W. L. (1932). *Amer. J. Dis. Child.*, **44**, 336.
Whitby, L. E. H., and Hynes, M. (1935). *J. Path. Bact.*, **40**, 219.

APPENDIX

The following scanty details were obtained about the two sisters, who died before this investigation.

M.B., the second child and eldest daughter, was born in 1939. She was pale, anaemic, and lethargic from birth. Her condition slowly worsened, but she was seen only by her local doctor, and was not admitted to hospital at any time. She died in 1944.

R.B., the third child and second eldest daughter, was born in 1940. She was normal until 2 years of age, when she began to show signs of increasing pallor and weakness. Her condition slowly deteriorated, and in June, 1947, she was admitted to hospital. Her father insisted upon her discharge after a month, and she died at home in 1947. Unfortunately her hospital records could not be traced, but the following haematological report was discovered in the laboratory files.

R.B.C.s, 2,380,000 per c.mm.; Hb, 36%; W.B.C.s, 8,200 per c.mm. A differential count gave polymorphs 29%, lymphocytes 45%, monocytes 9%, erythroblasts 25%. Aniso- and poikilocytosis were marked and there were numerous target cells and polychromatics.

Photographs of the two girls showed quite clearly that both had marked mongoloid facies.

THE DEVELOPMENT OF MEDITERRANEAN ANAEMIA

BY

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(RECEIVED FOR PUBLICATION JUNE 13, 1950)

Because of the rarity and the fact that mild forms of Mediterranean anaemia and the trait have only been recognized in recent years, opportunities for observing the development of the disease from its inception have been lacking. A recent investigation in Cyprus, where the condition is relatively common, fortuitously presented the opportunity of following two cases from birth.

The time of onset has been given as varying from shortly after birth up to the early years of life, usually the first two years. The disease may be present long before it is recognized, since increasing pallor is usually the first symptom. The presence of anaemia can, of course, be recognized by blood examination some time before pallor is noted clinically. It has also been shown that mild forms may in fact exist without the patient being aware of any disability. The case was observed during this investigation, of a young man aged 31 years with the disease in a mild form, who regularly cycled a distance of 33 miles over a rough road with no distress, is an example. He considered himself quite healthy.

Koch and Shapiro (1932) described a case which was recognized clinically at the age of 3 months. Fawdry (1947) diagnosed six cases by this age. Whipple and Bradford (1932) followed a case from birth, but unfortunately no haematological examination was made until the development of pallor at the age of 8 months. I can find no evidence in the literature of any cases followed up from birth with regular blood examinations.

While examining two children suffering from Mediterranean anaemia it was noted that their mothers were again pregnant. In view of the hereditary nature of the condition it was obviously desirable to examine the offspring as soon as possible after birth. S.K. was examined three days after she was born, and I.D. 35 days after birth. Both cases were followed up at intervals and they will be considered in detail.

Case Reports

S.K. Three days after birth her haemoglobin was 12·7 g. %. This is a definite anaemia considering the normal figure for that age. The film showed the characteristic features of the trait. There was a mild degree of anisocytosis and poikilocytosis; target cells were present and there was a reticulocytosis. There were no circulating normoblasts, and the changes were not as severe as would be found in the disease. At the age of 85 days circulating normoblasts were present, and the haemoglobin had fallen to 6·4 g. %. The mother did not as yet consider her child to be unwell, and she was quite satisfied with her progress thus far. The liver and spleen, however, were enlarged and easily palpable. Further observation at monthly intervals showed rapidly developing, severe anaemia, and the child died from fulminating bronchopneumonia at the age of 165 days. Detailed blood examinations were as follows.

Blood Examinations	First	Second	Third	Fourth
Age (days)	3	85	116	158
Hb. (g. %)	12·7	6·4	5·4	3·8
R.B.C. (mill. per c.mm.)	4·05	2·85	1·72	2·2
Reticulocytes	8%	12%	16%	14%
Normoblasts—				
early (per 100 W.B.C.)	0	27	152	125
late (per 100 W.B.C.)	0	6	50	137
total (per 100 W.B.C.)	0	33	202	262
Anisocytosis, poikilocytosis	+	++	+++	+++
Target cells	+	+	++	+
Ovalocytosis	+	+	+	++
Microcytosis	–	+	++	++
Fragility	Constant—0·42–0·12 g. NaCl.%			
Blood group				O
Total W.B.C. ..	7,000	17,400	24,500	24,400
Neutrophils ..	62%	20%	26%	33%
Stab cells	3%	6%	3%	8%
Juveniles	5%	8%	3%	7%
Lymphocytes ..	18%	62%	66%	39%
Monocytes ..	3%	2%	1%	3%
Eosinophils ..	9%	1%	1%	10%
Basophils	0%	1%	0%	0%

Figs. 1 and 2 show the changes in the blood films between the third and 116th days.

I.D. This case was first examined at the age of 35 days. The haemoglobin was then 8·9 g.%. Despite this degree of anaemia, there were no circulating normoblasts, and the film was characteristic of a severe degree

of the trait—rather like the first film of the previous case. Though the haemoglobin had fallen to 7·1 g. % by the 71st day, the mother was still satisfied with her child's progress. Enlargement of the spleen was recognized at this stage. At 151 days the mother thought the child pale, but had no specific complaint. Detailed blood examinations were as follows.

Blood Examinations	First	Second	Third
Age (days)	35	71	151
Hb. (g. %)	8·9	7·1	6·5
R.B.C. (mill. per c.mm.) ..	3·4	2·8	3·2
Reticulocytes	7%		
Normoblasts—			
early (per 100 W.B.C.)	0	2	4
late (per 100 W.B.C.)	0	3	3
total (per 100 W.B.C.)	0	5	7
Anisocytosis, poikilocytosis	+	++	+++
Target cells	++	++	+
Ovalocytosis	+	+	++
Microcytosis	+	++	++
Fragility	Constant—0·36–0·18 g. NaCl. %		
Blood group			O
Total W.B.C.s	7,200	9,000	12,900
Neutrophils	27%	17%	37%
Stab cells	0%	1%	1%
Juveniles	2%	5%	4%
Lymphocytes	68%	73%	54%
Monocytes	2%	2%	2%
Eosinophils	1%	1%	2%
Basophils	0%	1%	0%

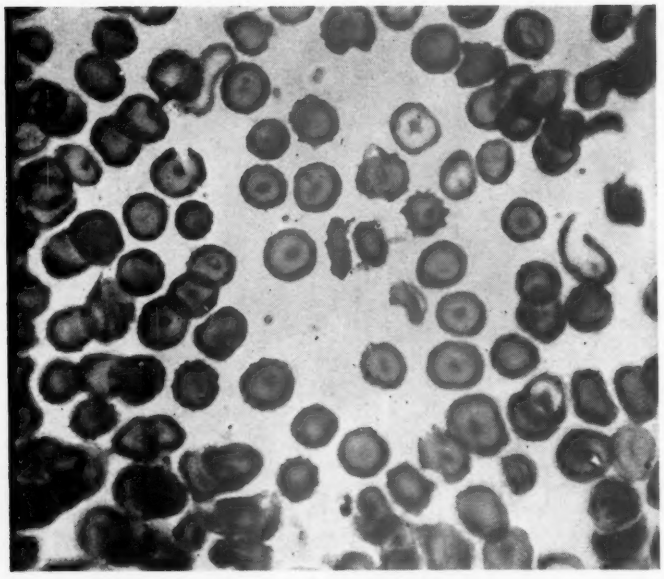

FIG. 1.—Blood film of S.K., aged 3 days. This film shows the typical features of the trait. Mild anisocytosis and poikilocytosis, target cells, and ovalocytes are seen. (× 850.)

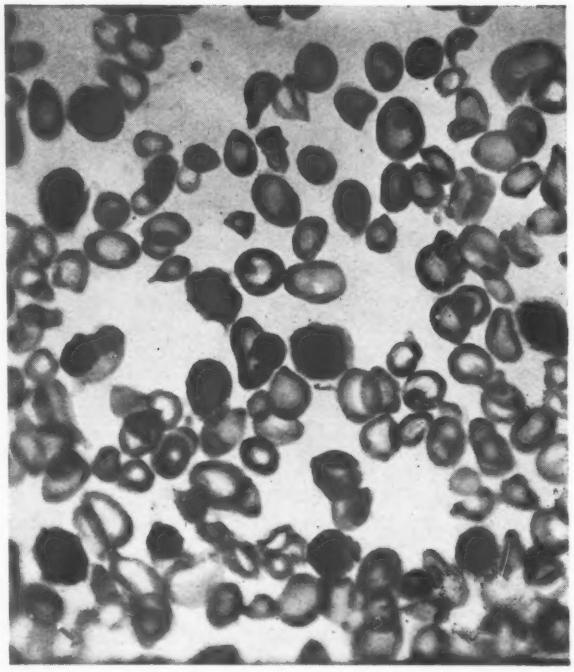

FIG. 2.—Blood film of S.K., aged 116 days. Anisocytosis and poikilocytosis have increased and normoblasts, particularly early forms, are present in the peripheral blood. There is marked hypochromia.

Discussion

The aetiology of Mediterranean anaemia has long required clarification. The development of the disease in these two cases can be correlated with recent work relating to this problem.

Though Mediterranean anaemia is a typical haemolytic anaemia, the work of Fawdry (1947) showed that there were no abnormal haemolysins in the plasma. The survival of erythrocytes from a healthy donor transfused into a case of Mediterranean anaemia was within normal limits. When blood from a case of the trait of the disease was used for the transfusion, the erythrocytes were haemolysed more rapidly than normal. This suggests that the abnormality lies in the erythrocyte rather than in the serum. Valentine and Neel (1944) point out the undesirability of transfusion of a case from one of its parents, since these are affected with the trait.

Pauling, Itano, Singer, and Wells (1949) have shown that in sickle cell anaemia an abnormal haemoglobin is present. In patients suffering from the disease all the haemoglobin is of this abnormal type, and in individuals exhibiting merely the trait of the disease only a proportion of the haemoglobin is abnormal. As is suggested (*Lancet*, 1950), other anaemias may be explained on these grounds and Mediterranean anaemia is clearly one of them.

If it is accepted that the defect in Mediterranean anaemia is in the erythrocyte, possibly with an abnormal haemoglobin content, then the following hypothesis, in the light of the two cases described, may be advanced to elucidate the factors underlying the development of the disease. It is suggested that there is a defect in haemoglobin synthesis, due to the absence of some agent acting as a catalyst. Such an absence would have to be relative in order to produce that gradation in the anaemia seen between the mild and the severe cases. From a genetic point of view, since the trait is inherited as a Mendelian dominant, this variable defect would be the link with the mutated gene causing the disease, and would be the fundamental error in Mediterranean anaemia. If this is correct, one would expect the development of the disease in the first few months of life. The disease will not be fully developed at birth, since the deficient factor can be partially supplied by the mother, herself having the trait of the disease. As the source of this factor is cut off at birth, anaemia will gradually develop as the supply is used up in the early months of life. The infant's haemoglobin will fall to a level dependent on how far the infant can supply the factor from its own resources, and clearly this level will be maintained for the rest of the patient's life, except in so far as it is affected by external influences such as infections, or conditions, such as nephritis, producing anaemia, and other environmental factors. This theory will have to be tested by following other cases from birth. The age of onset judged clinically is of no value; haematological examination carried out regularly from birth is required. Carrying the theory further, cases of the trait born of mothers with the trait and normal fathers should show the trait at birth. If the father has the trait and the mother is normal, offspring who develop the trait should be normal at birth, since the normal mother can supply the deficient factor, but the trait should develop in the course of the next few months. This theory has only been elaborated since leaving Cyprus, but it would be a simple matter to put it to the test.

Another theory to be considered is suggested by the work of Dacie and Mollison (1949). They transfused blood from a patient with nocturnal haemoglobinuria into an adult and an infant 38 days old. They showed that in both cases the transfused cells were eliminated more rapidly than normal, but the rate of elimination was considerably greater in the adult than in the infant, the significant point being that the haemolytic activity of the infant's serum was less than that of the adult. Applying this point to the problem at issue it is possible that at birth the haemolytic activity of the serum is small and hence the anaemia is not fully developed. As the haemolytic activity of the serum increases with age, so the strain on the bone marrow increases and the anaemia becomes apparent. As, however, the haemolytic activity of the serum is not likely to be materially increased in the early months of life when the anaemia is developing, this theory is discarded in favour of the former.

Summary

Two cases of Mediterranean anaemia have been observed haematologically from shortly after birth, and the development of the disease has been demonstrated in the early months of life.

Possible theories for the causation and development of Mediterranean anaemia are discussed.

References

Dacie, J. V., and Mollison, P. L. (1949). *Lancet*, **1**, 390.
Fawdry, A. L. (1947). Annual report of D.M.S. Cyprus.
Koch, L. A., and Shapiro, B. (1932). *Amer. J. Dis. Child.*, **44**, 318.
Lancet (1950), **1**, 770.
Pauling, L., Itano, H. A., Singer, S. J., and Wells, I. C. (1949). *Science*. **110**, 543.
Valentine, W. N., and Neel, J. V. (1944). *Arch. intern. Med.*, **74**, 185.
Whipple, G. H., and Bradford, W. L. (1932). *Amer. J. Dis. Child.*, **44**, 336.

A CASE OF FANCONI'S ANAEMIA

BY

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In 1927 Fanconi described under the title ' familial pernicious-like anaemia in children ' three brothers with fatal refractory anaemia associated with pigmentation of the skin, testicular atrophy, microcephaly, underdevelopment, squint, and increased tendon jerks. In the same paper he reported a case with muscular dystrophy, pigmentation, testicular hypoplasia, microcephaly, and anaemia of a similar type which remitted spontaneously while the patient was in hospital. The parents of this child were said to be brother and sister. Sporadic and familial cases presenting the triad of severe refractory anaemia, pigmentation, and congenital anomalies have been noted by Uehlinger (1929), Émile-Weil (1938), Hjorth (1940), van Leeuwen (1933), Dacie and Gilpin (1944), Estren, Suess, and Dameshek (1947), and Diamond (1950). A further case showing anaemia, pigmentation, congenital dislocation of the hips, and an anomaly of the left kidney is reported here.

Case Report

M.S., a girl, was born on April 8, 1943. She had always bruised easily but otherwise made normal progress until she began to walk at 2 years of age, when a waddling gait led to the diagnosis of congenital dislocation of both hips. She was admitted to hospital on numerous occasions for treatment of this condition. In December, 1946, she had measles followed by bilateral otorrhoea; she afterwards lost weight, and her general health, which had previously been good, deteriorated. A blood count in May, 1947, during one of her admissions to hospital, showed Hb. 68% (Haldane); red blood cells, 3·3 m. per c.mm.; C.I. 1·0; slight anisocytosis; white blood cells, 5,100 per c.mm. (polymorphs 39%, lymphocytes 59%, monocytes 1%, basophils 1%). A blood transfusion brought the haemoglobin up to 78% (Haldane) and improved the child's general condition.

In April, 1950, at the age of 7 years, she was admitted to Westminster Children's Hospital complaining of fatigue and breathlessness on going uphill. Her legs had always ached a great deal but this aching had become more marked recently. There had been two

Table
Haematological Findings

Date	Hb. (Haldane) (%)	R.B.C. (m. per c.mm.)	W.B.C. (per c.mm.)	Polymorphs	Lymphocytes	Monocytes	Platelets (per c.mm.)	Reticulocytes (%)	Blood Transfusion
6.4.50	28	1·1	4,400	2,200	2,200	—	40,000	2	1 pint
12.4.50	45	2·2	—	—	—	—	72,000	—	—
14.4.50	—	—	—	—	—	—	—	—	1 pint
18.4.50	78	3·6	—	—	—	—	50,000	—	—
5.5.50	56	—	4,600	2,100	2,300	200	—	—	—
15.5.50	48	—	3,600	1,200	2,200	200	—	—	—
12.6.50	48	—	3,200	1,100	1,900	200	—	—	18 oz.
13.6.50	66	—	5,000	2,000	2,700	300	98,000	3	—
20.6.50	58	2·8	3,200	1,200	1,900	100	98,000	3	

violent epistaxes in the past six months and her appetite had been poor in the past few days. The mother had just recently noticed the pallor: she said that the child became very brown in the sun but had not thought the pigmentation to be otherwise remarkable. The patient was backward at school and this was attributed to her deafness. Apart from occasional attacks of bronchitis, and the measles and otorrhoea noted above, there had been no previous illness. The parents and the patient's brother, aged 4 years, were quite well. The maternal grandmother was said to have had pernicious anaemia and diabetes but otherwise there was no family history of blood disease or congenital deformities. The parents were first cousins, and their blood groups, determined subsequently, were: father group O, Rhesus negative, genotype OO; mother group A, Rhesus positive, genotype A_1O or A_1A_2. The patient was group A_1, Rhesus positive, genotype A_1O.

On examination she was seen to be a pale child, looking rather older than her 7 years (Fig. 1), with brown pigmentation over the whole body, darkest over the flexures, the neck, the genitalia, and around the eyes, and fading to a brownish-yellow over the face, arms and legs. There was a bruise on the inner side of the right ankle and a few purpuric spots in the right antecubital fossa where blood had been taken an hour earlier. She was thin and undersized, very nervous, and tended to cry easily. Her height was 35·5 in., and her weight 38 lb. 8 oz. The head circumference was 19·5 in. The temperature was 99·4, pulse 140, and respiration 28. The ear drums were normal. There was no pigmentation in the mouth; the tongue was clean, and there was a small bleeding point on the right tonsil. There were a few carious teeth. There was a loud systolic murmur, maximal at the apex, and also heard posteriorly over the right lung, but no clinical evidence of cardiac enlargement. There was a convergent strabismus; the fundi oculorum were not pigmented and the discs were pale. All tendon jerks were brisk but there was no clonus. The liver and spleen were not palpable and there were no enlarged lymph nodes. There was a sacrococcygeal sinus.

FIG. 1.—The patient.

The results of investigations at this stage were as follows.

A blood count gave Hb. 28% (Haldane), R.B.Cs. 1·1 m. per c.mm., C.I. 1·3, packed cell volume 11%, mean cell volume 100 c.μ, mean cell haemoglobin concentration 35%, reticulocytes 2%, W.B.C.s 4,400 per c.mm. (polymorphs 51%, lymphocytes 49%), platelets 40,000 per c.mm. There was no blood and no excess urobilinogen in the urine. There was occult blood in the faeces, and 84 mg. % urobilinogen.

A sternal marrow puncture was performed by Dr. J. G. Humble on April 6, 1950, and reported by him as follows:

The total nucleated count was 45,000 per c.mm. A differential count on 500 cells showed myeloblasts 0%, promyelocytes 2%, neutrophil myelocytes 11·8% (4% of these showed mitoses), neutrophil metamyelocytes 10·6%, eosinophil myelocytes 0·8%, neutrophil polymorphs 17·6%, eosinophils 1·4%, lymphocytes 31·8%, plasma cells 1·8%, monocytes 2%, reticulo-endothelial cells 1·2%, no megakaryocytes, haemocytoblasts 0·4%, proerythroblasts 0·2%, normoblasts A 4·6%, normoblasts B 10·8% (6% of these showed mitoses), normoblasts C 3%. There was arrest of maturation of the red and white cell series at the early normoblast and promyelocyte level.

On April 6 the child was given a transfusion of one pint of fresh blood, and a further pint was given on April 14. On April 17 the haemoglobin was 78% (Haldane). From then until June 12, when she was given another 18 oz. of blood, the haemoglobin fell at the rate of about 1% per day. She was discharged home on June 20, to be observed by her own doctor. The haematological course is shown in the accompanying table.

After the first two transfusions the pyrexia and tachycardia gradually settled down, the child's general condition improved, and she became more cheerful. Occasional crops of petechiae in the mouth and on the trunk and limbs, and bleeding from the gums and right tonsil were noted during the first month. There was haematuria between April 4 and April 20. She had an epistaxis on April 16, and bleeding from the right ear on April 23, after which there were no haemorrhagic

manifestations except for slight oozing from the gums. There were a few urticarial spots on the right cheek and left wrist on April 15. Ferrous sulphate, a proteolysed liver extract ('hepamino'), folic acid, and vitamin B_{12} had no effect on the anaemia or the reticulocytes.

Results of other investigations were as follows:

Serum bilirubin level 0·0 mg. %; serum sodium level 324 mg. %; bleeding time (Duke) 5 minutes; clotting time (Lee and White) 4 minutes; capillary resistance test (Hess) positive; red cell fragility normal. An adrenaline response test (Benda, 1930) showed the usual immediate increase in circulating leucocytes due to contraction of the spleen after the administration of 13 minims adrenaline subcutaneously. There was no secondary rise of myeloid cells attributable to bone-marrow stimulation.

A 'hyalase' subcutaneous pyelogram showed a normal kidney and ureter on the right but no dye was excreted on the left. A retrograde pyelogram on the left side outlined an apparently normal but presumably unfunctioning kidney lying in the pelvis. Radiographs of all bones showed no abnormality apart from the dislocated hips and some coarse trabeculation of the bones of the feet. A chest radiograph was normal.

Discussion

That this condition is inherited is suggested by its occurrence in siblings (Fanconi, 1927; Émile-Weil, 1938; Hjorth, 1940), in an incestuous brother and sister mating (Fanconi), and in cousin marriages (Dacie and Gilpin, 1944; and this case). In Hjorth's cases the brother had a clubfoot and the sister dislocation of the hip. One maternal cousin had a congenital dislocation of the hip and another had a clubfoot, absent calcaneus, and a dislocated patella. A paternal cousin had absent thumbs and was mentally defective. Estren and Dameshek (1947) consider that the cases of familial hypoplastic anaemia described by them may belong to the same group. There is support for this view in the cases described by Dacie and Gilpin: one brother had anaemia, pigmentation and congenital defects, whereas the other had anaemia only. These authors also mention that a sib of the mother and a sib of the father had married one another and produced a child who died of aplastic anaemia.

Anomalies of thumbs, kidneys, and testes have been frequently reported in these cases. In the four cases previously described in which the blood group has been mentioned it was group A as in this case.

Haemosiderosis of the internal organs is a usual finding at necropsy, but the skin pigment appears to be melanin (Fanconi, 1927; Uehlinger, 1929). Melanosis of the intestine was noted by Hjorth (1940).

This condition must be distinguished from Fanconi's syndrome of rickets, aminoaciduria, and glycosuria (Fanconi, 1936) which is quite a different disease.

The prognosis is bad: all patients previously described showing the full syndrome have died except the case of Estren *et al.* which was slightly improved during a follow-up period of several months after splenectomy, and Fanconi's case mentioned above where the anaemia appeared to be transient. Splenectomy had no effect in van Leeuwen's case apart from a temporary rise in platelets. The spleen was removed in Dacie and Gilpin's case showing anaemia only and the patient ultimately recovered (Dacie, 1950). Splenectomy was followed by some improvement in one case of familial hypoplastic anaemia described by Estren and Dameshek. In the case described here splenectomy might be considered since the bone-marrow picture and the result of the adrenaline response test are consistent with a splenic haematopenia. Repeated blood transfusion to keep the patient alive in the hope of a remission is the only other treatment which offers any prospect of success.

Summary

A case of Fanconi anaemia is described showing pigmentation of the skin, congenital dislocation of the hips, an abnormality of the left kidney, convergent strabismus, a sacrococcygeal sinus, underdevelopment, mental backwardness, and anaemia with granulopenia and thrombopenia. The parents were first cousins. The aetiology, prognosis, and treatment are briefly discussed.

I wish to thank Dr. Charles F. Harris and Mr. David Levi for permission to use the case notes and publish the case, Dr. J. G. Humble for the marrow report and much help and advice, Dr. L. J. Rae for the radiological reports, Dr. K. Goldsmith for the genotyping, Professor N. F. Maclagan and the staff of the department of Chemical Pathology, Westminster Medical School, for certain of the biochemical investigations, and the photographic department, Westminster Medical School, for the photograph.

References

Benda, R. (1930). *Ann. Méd.*, **27**, 190.
Dacie, J. V. (1950). Personal communication.
——, and Gilpin, A. (1944). *Archives of Disease in Childhood*, **19**, 155.
Diamond, L. K. (1950). In Mitchell-Nelson 'Text-book of Pediatrics,' 5th ed., p. 1128. Philadelphia.
Émile-Weil, P. (1938). *Sang*, **12**, 369.
Estren, S., and Dameshek, W. (1947). *Amer. J. Dis. Child.*, **73**, 671.
——, Suess, J. F., and Dameshek, W. (1947). *Blood*, **2**, 85.
Fanconi, G. (1927). *Jb. Kinderheilk.*, **117**, 257.
—— (1936). *Ibid.*, **147**, 299.
Hjorth, P. (1940). *Nord. Med.*, **7**, 1313.
Leeuwen, H. C. van (1933). *Folia haemat., Lpz.*, **49**, 434.
Uehlinger, E. (1929). *Klin. Wschr.*, **8**, 1501.

ACHOLURIC JAUNDICE IN A NEWBORN INFANT

BY

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Congenital familial haemolytic anaemia in newborn infants has come to be regarded almost as synonymous with erythroblastosis foetalis in one of its varieties. The following case is reported as a reminder that the picture of an acute haemolytic anaemia in early life can be due to other causes.

Case Report

Mrs. C., the mother, of the affected infant, came under observation for the first time in 1940, with a history of chronic backache, puffiness of the eyes, and frequency of micturition. These symptoms were discovered to be due to pyelitis which was treated with sulphonamide, with marked improvement. At this time she was noticed to be slightly jaundiced and her spleen was enlarged to three fingers' breadth below the costal margin. A routine blood count showed haemoglobin 45%, red blood cells 3,060,000, colour index 0·73. The red cells were said to be normal in size and shape in stained films. She was discharged home after four weeks in hospital with instructions to take iron at home.

Her first child was born in 1941. The notes of this delivery were unfortunately lost owing to the war-time dislocation of the hospital's routine. The infant was apparently normal but the mother received several transfusions in the lying-in period.

The second pregnancy in 1943 was complicated by toxaemia with oedema and albuminuria. She was admitted for treatment and was found to be grossly anaemic, her haemoglobin being 23%. She was again transfused and went into premature labour which resulted in the birth of a male infant weighing 4 lb. 15 oz. This infant progressed satisfactorily until the sixteenth day when he was noted to be very pale; the infant died suddenly on the following day. Post-mortem examination revealed the cause of death to have been bronchopneumonia complicating haemolytic anaemia which was attributed to erythroblastosis foetalis.

After this confinement the mother's blood was fully investigated and she was found to have typical acholuric jaundice. Her red cells showed definite spherocytosis (mean corpuscular average thickness 3·7μ). Fragility tests in saline solutions showed haemolysis beginning at 0·65% and almost complete at 0·45%. Early in 1944 her spleen was removed and microscopic examination was said to show a 'structure typical of acholuric jaundice'.

The third pregnancy terminated in 1948 in the birth of a normal full-term male infant. Repeated blood investigations on this infant (including fragility tests) failed to reveal any evidence of a blood dyscrasia.

The fourth pregnancy also went to term and resulted in the birth of a mature female infant. The mother's Wassermann reaction was negative in this as in the other pregnancies. This child was carefully watched and the following blood values were obtained:

Cord blood at birth.	Hb. 15·6 g.%.	R.B.C. 4,190,000.
On the second day.	Hb. 23·7 g.%.	R.B.C. 6,320,000.
On the fourth day.	Hb. 23·4 g.%.	R.B.C. 7,450,000.
On the seventh day.	Hb. 17·1 g.%.	R.B.C. 5,050,000.
On the tenth day.	Hb. 18·3 g.%.	R.B.C. 6,980,000.

Fragility tests on the sixth day gave results almost identical with the mother's, haemolysis beginning at 0·65% and being practically complete at 0·45%. Fragility tests on the mother's erythrocytes showed the persistence of increased fragility; haemolysis began at 0·6% saline and was almost complete at 0·45%. The infant appeared perfectly normal on the fourteenth day in spite of the undoubted evidence of abnormality of the erythrocytes and was discharged with the mother. Three days later, however, she was seen again, and on this occasion the findings were Hb. 7·1g. %; R.B.C. 1,890,000; mean cell diameter 5·7μ; mean corpuscular average thickness 3·1μ; reticulocytes 5%. The infant was pale but not appreciably jaundiced and the spleen was just palpable. A transfusion of whole blood was given and the child discharged. She was readmitted on the thirty-seventh day of life, having had a further haemolysis. The findings were Hb. 9·9 g. %; R.B.C. 2,950,000. The baby was pale but again not perceptibly jaundiced. A further transfusion was given and she was discharged. Since then she has been seen repeatedly for a period of four months and no further haemolytic episodes have occurred.

Mrs. C.'s relatives were investigated at the time the diagnosis was established in 1943, and no other affected members of her family were discovered. Her serological groups are given by the Regional Transfusion Laboratories as Group O, Rh positive. The Regional Transfusion Officer comments:

'Mrs. C. was first referred to us during her 1947 pregnancy and later in her 1950 pregnancy. At no time have we been able to demonstrate immune antibodies in her serum nor have the infants shown any signs of immunization in that the direct Coombs tests have always been negative. Mrs. C.'s red cells contain the

antigen D^u and her children have been D positive. Since D^u is a variant of D, no immunization occurs.'

The two surviving children of the previous pregnancies have been reinvestigated since the birth of the fourth child and their blood has been found to be normal in all respects.

There is no doubt that this infant is a case of familial haemolytic anaemia or acholuric jaundice. The diagnosis rests on (1) the strong family history, (2) the occurrence of considerable blood destruction within a very short period, (3) the characteristic increase in fragility of the child's erythrocytes and the spherocytosis, (4) the exclusion of other causes of haemolysis at this age.

Discussion

Acholuric jaundice is recognized to be due to an inherited defect of the erythron, which is demonstrated by the abnormal erythropoiesis seen in bone marrow smears, by the abnormal contour of the erythrocytes in the circulating blood, by their excessive fragility in saline solutions, and by their liability to rapid destruction in the body. It is known that these characteristics persist in spite of clinical cure of the disease by splenectomy, and the examination of near relatives of frank cases has often revealed similar abnormalities in spite of the absence of symptoms. It is remarkable, however, how rarely this abnormality manifests itself in infancy. There is considerable variety of opinion about the frequency of clinical manifestations in early life. The following opinions have been encountered in standard text-books.

> 'Cases have been recorded in the first few hours of life. . . . The youngest recognized case in the author's series was 14 days old.' (Vaughan, 1936.)
>
> '[Symptoms] may appear at birth or shortly afterwards.' (Wintrobe, 1942.)
>
> 'Jaundice, which is the most striking feature, may start at birth, or very soon afterwards; it is rarely delayed till after infancy.' (Gregory, 1933.)
>
> 'The disease may manifest itself any time between infancy and adolescence.' (Sanford, 1948.)
>
> 'The active form of the disease often does not manifest itself in infancy, but it may be present even at birth or may develop at any time.' (Josephs, 1940.)
>
> 'It can be observed in earliest childhood though definite symptoms appear usually at the beginning of the school age or shortly before.' (Opitz, 1935.)
>
> 'The disease seldom becomes apparent in infancy.' (Cooley, 1949.)
>
> 'Clinical manifestations are relatively rare in infants.' (Diamond, 1950.)
>
> 'Symptoms may appear at any age but are rare in infancy.' (Whitby and Newns, 1949.)
>
> 'The resulting haemolytic anaemia becomes manifest in early life but rarely in infancy.' (Kugelmass, 1941.)

There is little indication in most of these assertions of the occurrence of the disease in the neonatal period. The term 'infancy' so frequently used has no specific connotation. It may refer to the first year, or to the first two years of life.

Of reported cases of the active disease at or shortly after birth there is not a large number. Gripwall (1938) reported 31 cases in detail. Of these three were said to have had jaundice from birth but they were not seen until the ages of 10 years, 17 years, and 23 years, and none of them was apparently sufficiently ill in the early years of life to require medical care. Thompson (1939) records 43 cases from a special clinic. From his tables it appears that the youngest case was a child of 8 months, who was said to have been jaundiced for six months. Debré, Lamy, Sée, and Schrameck (1938), record 20 cases observed in a period of 12 years in Paris. The youngest was 4 months old at the time of discovery. Dawson (1931) in his Hume lectures on haemolytic icterus gives a genealogical table of an affected family in which four of the children were said to have been born jaundiced. No further details of these are given and the earliest onset of symptoms recorded in his case reports is at 2 years of age. Parsons (1938) in an extensive review of 'The Haemolytic Anaemias of Childhood' devotes only a small space to acholuric jaundice. He records two cases (in cousins) in whom symptoms began before the third and fourth months. Newns (1950) has collected 22 cases from the records of The Hospital for Sick Children, Great Ormond Street. Of these nine certainly, and one probably, exhibited symptoms before the age of 1 year, and in three others the diagnosis was established by the age of 1 year. Three of these cases were seen in the first month of life—one at one week, one at 10 days, and the third at one month. In four others symptoms were reported shortly after birth but the children were not seen until some time later. Fallon (1943) records seven cases of whom five were said to have had symptoms in early infancy. One was anaemic, with a reticulocytosis of 11% at 2 months; a second became jaundiced at two months and at 4 months had marked anaemia with reticulocytosis; the third was definitely anaemic at the age of $3\frac{1}{2}$ months; the fourth case was said to have had attacks of jaundice since birth but did not come under observation until the age of 14 years; her fifth case is a curious one. The infant became jaundiced and anaemic at the age of 12 days and splenectomy was performed at the age of 2 months. There is no record of fragility tests and neither the clinical condition nor the blood values were improved by the operation. Meulengracht (1938) states that, 'As far as I know, no case has ever been observed

in which this effect [rise in haemoglobin content and erythrocyte count] failed to appear; nor has there been recorded any such case where there was a relapse of the anaemia subsequent to splenectomy.' There must therefore be considerable doubt about the accuracy of the diagnosis in this case of Fallon's. Diamond (1937) reported six cases of which the youngest was an infant of 4½ months whose symptoms began at the age of 2½ months. Josephs (1938) reported four cases in only one of which did the symptoms begin shortly after birth and he comments: 'This is one of the few cases in which the evidence is fairly convincing that the disease was present at birth.' Abt (1940) gave an account of three cases in two of whom the disease started at 4½ months; in the third case pallor and jaundice had been noticed from birth.

Detailed histories of cases showing evidence of the disease in the first month of life are recorded by Josephs (1938) (one case), Abt (1940) (one case), Conrad and Schmidt (1946) (one case), Schiff (1938) (one case), Hawksley (1934) (one case), Fallon (1943) (one case—diagnosis doubtful), and Newns (1950) (three cases). Of these Hawksley's is the most similar to the present one. The infant was the third affected child of its parents (two brothers had had their spleens removed because of acholuric jaundice); the infant appeared normal at birth; increased fragility and microcytosis were demonstrated on the second day of life; pallor was marked on the thirty-seventh day and the spleen was just palpable at the age of 7 weeks. In this case, as in the present one, the diagnosis was made before the onset of symptoms.

The present case appears to be the first in which the disease manifested itself in more than one member of the second affected generation in early infancy. It seems to be rare to obtain a positive family history when the disease appears in early infancy. Abt, writing in 1940, stated that 'the occurrence of this condition in cousins, mentioned by Parsons, is the only instance in which a familial history has been noted when the disease occurred in early infancy'. This is not quite correct, since Hawksley reported his case in 1934, but it may be taken as indicating the rarity of the appearance of the disease in the infants of affected families.

As regards symptomatology, David and Minot (1944) write that 'in the infant icterus is usually slight—pallor and splenomegaly being the most outstanding physical findings'. This is supported by Abt (1940) who says, 'When the illness is first manifested in early infancy, jaundice may be entirely absent, even though there is indisputable evidence of considerable increase in destruction of blood.' In the cases of Hawksley, Schiff, Conrad, and Schmidt, and in two of Newns' cases pallor is recorded as the dominant symptom. This casts some doubt on the cases, such as those of Gripwall and of Dawson, in whom there was only a history of persistent jaundice after birth. Neonatal jaundice may be marked and persistent without any evidence of undue haemolysis. Still (1924) mentions an infant in whom it persisted for 9½ weeks.

The youngest infant submitted to splenectomy appears to be the case of Fallon's in whom it was performed at the age of 2 months. The operation was not successful, in that the condition was not relieved. Newns (1950) notes a case in which splenectomy was carried out at 2½ months. The infant survived the operation but died of bronchopneumonia and suprarenal haemorrhage at the age of 3½ months. The earliest successful operation is that recorded by Conrad and Schmidt (1946) at the age of 10 weeks. Diamond (1937) and David and Minot (1944) report successful operations at the ages of 4½ and 5 months. Abt (1940) advocates early splenectomy, and Fallon (1943) considers that if operation is delayed recovery may be incomplete.

In spite of assertions to the contrary, it would appear that the occurrence of clinically significant haemolysis in infants born with the inherited abnormality of the erythron which is the characteristic feature of acholuric jaundice is a rare event. The present case appears to be the first recorded in which the disease, directly transmitted from an affected parent, has given rise to severe haemolytic anaemia in the neonatal period in more than one child.

Summary

A case is reported in which the inheritance of acholuric jaundice is demonstrated from mother to child in two of four children of an affected woman.

In both infants the disease became clinically apparent in the neonatal period.

This sequence of events is rare, if not unique.

I am indebted to Dr. D. V. Hubble, under whose care the infant was, not only for permission to publish, but for suggesting that this report be made. The numerous haematological investigations were carried out in the laboratory of the hospital under the supervision of Dr. G. R. Osborn. Dr. R. H. Malone, Regional Transfusion Officer to the Sheffield Hospital Region, provided the serological report. I am grateful to Dr. G. H. Newns for allowing me to see his material. This will be published at a later date.

REFERENCES

Abt, A. F. (1940). *Amer. J. Dis. Child.*, **60**, 812.
Conrad, E., and Schmidt, R. E. (1946). *Ibid.*, **72**, 731.
Cooley, T. B. (1949). In Brennemann, 'Practice of Pediatrics'. vol. 3, ch. 16, p. 38. Hagerstown, Maryland.
David, J. K., and Minot, A. S. (1944). *Amer. J. Dis. Child.*, **68**, 327.

Dawson of Penn, Lord (1931). *Brit. med. J.*, **1**, 921.
Debré, R., Lamy, M., Sée, G., and Schrameck, G. (1938). *Amer. J. Dis. Chi'd.*, **56**, 1189.
Diamond, L. K. (1937). *Med. Clin. N. Amer.*, **21**, 401.
—— (1950). In Mitchell-Nelson, 'Textbook of Pediatrics,' 5th ed., p. 1110. Philadelphia.
Fallon, M. (1943). *J. Pediat.*, **23**, 721.
Gregory, H. H. C. (1933). In Parsons and Barling, 'Diseases of Infancy and Childhood,' vol. 1, p. 852. London.
Gripwall, E. (1938). *Acta med. scand.*, Suppl. 96.
Hawksley, J. C. (1934). *Proc. roy. Soc. Med.*, **27**, 942.
Josephs, H. W. (1938). *Bull. Johns Hopk. Hosp.*, **62**, 25.
—— (1940). In Holt and McIntosh, 'Diseases of Infancy and Childhood,' 11th ed., p. 629. New York.
Kugelmass, I. N. (1941). 'Blood Disorders in Children,' p. 258. London.
Meulengracht, E. (1938). In 'Handbook of Hematology,' ed. Downey, H., vol. 3, p. 2281. New York.
Newns, G. H. (1950). Personal communication.
Opitz, H. (1935). In Pfaundler and Schlossmann, 'The Diseases of Children,' ed. Peterman, vol. 2, p. 201. Philadelphia.
Parsons, L. G. (1938). *Lancet*, **2**, 1395.
Sanford, H. N. (1948). In Grulee and Eley, 'The Child in Health and Disease', p. 470. Baltimore.
Schiff, E. (1938). *Archives of Disease in Childhood*, **13**, 264.
Still, G. F. (1924). 'Common Disorders and Diseases of Childhood,' 4th ed., p. 336. London.
Thompson, W. P. (1939). *Bull. N.Y. Acad. Med.*, **15**, 177.
Whitby, L. E. H., Newns, G. H. (1949). In Garrod, Batten and Thursfield, 'Diseases of Children,' 4th ed., vol. 2, p. 727. London.
Wintrobe, M. M. (1942). 'Clinical Hematology,' p. 389. London.
Vaughan, J. M. (1936). 'The Anaemias,' 2nd ed., p. 229. London.

CARDIAC CONCENTRIC HYPERTROPHY IN CHILDREN WITH HYDROCEPHALUS DUE TO TUBERCULOUS MENINGITIS

BY

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During a necropsy on a child with internal hydrocephalus due to tuberculous meningitis, concentric hypertrophy of the left ventricle of the heart was noticed. Since that observation further cadavera were examined in greater detail for evidence of hypertension. In six out of a consecutive series of 16 deaths from tuberculous meningitis treated with streptomycin at the Sheffield Children's Hospital evidence was found suggesting hypertension.

Case Summaries

Case 1. The child's illness began with a cough at the age of 17 months, and he developed signs of tuberculous meningitis five months later. He had been undergoing streptomycin treatment for 18 months before death at the age of 3 years and 1 month.

At necropsy, the body was seen to be emaciated. There was opisthotonos, and the limbs were in an extreme spastic posture. There was marked internal hydrocephalus with much exudate at the base of the brain and over the cisterna magna. There was dilatation of the fourth ventricle with thinning of the pons and medulla (Fig. 1). All the viscera appeared to be wasted with the exception of the left ventricle of the heart. The liver weighed 384 g. compared with the normal weight for that age of 420 g. (Coppoletta and Wolbach, 1933); the kidneys (together), 75 g. (normal 97 g.); heart, 59 g. (normal 59 g.). The left ventricle appeared to be concentrically hypertrophied, the muscle being 14 mm. thick (Fig. 2). No valvular abnormalities were found.

FIG. 1.—The fourth ventricle and pons from Case 1, showing thinning of the floor of the fourth ventricle, and exudate on the lower anterior surface of the pons and medulla (× 1).

FIG. 2.—Transverse section of the ventricles of the heart of Case 1 (× 1).

Case 2. Tuberculous meningitis began a month before treatment started. The child died, aged 2 years 8 months, after four months' streptomycin treatment. Teeth grinding and twitching began a month before death.

At necropsy the body was seen to be wasted and in a spastic posture. There was extreme flattening of the cerebral cortex with marked internal hydrocephalus, the cortex being 1-1·5 cm. thick. The circulation of the cerebrospinal fluid appeared to be obstructed at the level of the tentorium. All the viscera appeared wasted. The liver weighed 328 g. (normal 400 g.); the kidneys, 87 g. (normal 95 g.). The heart showed concentric

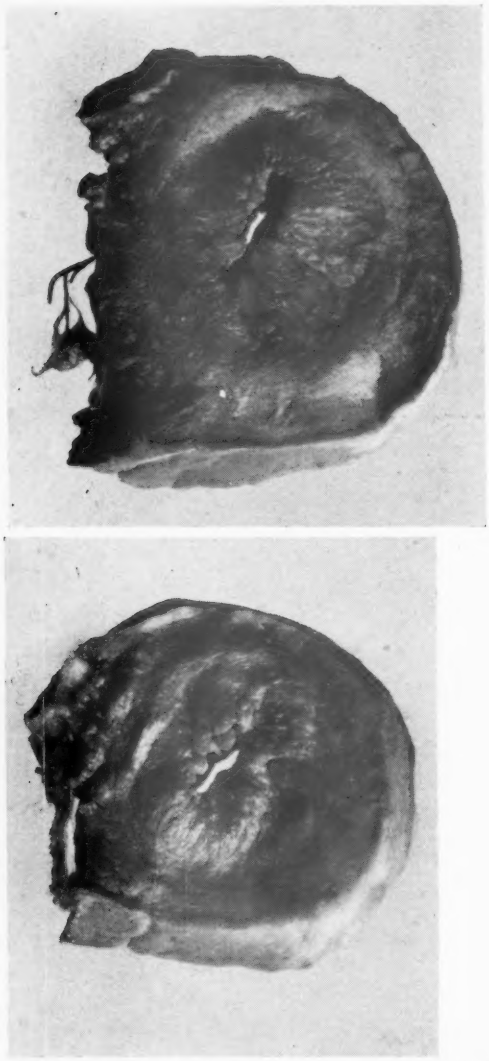

FIG. 3.—Transverse section of the left ventricle of Case 2 (× 1).

thickening of the left ventricle (Fig. 3), the muscle being 12-18 mm. thick. No abnormality was seen in the valves or great vessels. The heart weighed 51 g. (normal 58 g.).

Case 3. A boy aged 3½ years at death had been treated with streptomycin for 2½ months for tuberculous meningitis.

At necropsy there was marked hydrocephalus with thick fibrinous exudate about the base of the brain appearing to obliterate the cisterna magna. Many small areas of encephalomalacia were present. The heart weighed 64 g. (normal 61 g.), and showed some thickening of the left ventricle. Histology showed vessels in the liver and kidney with fibrinous degeneration of the muscle (Figs. 4 and 5).

Case 4. A boy, aged 9 years, fell ill with tuberculous meningitis four months before death. In the later stages contractions developed and a state of catatonic stupor.

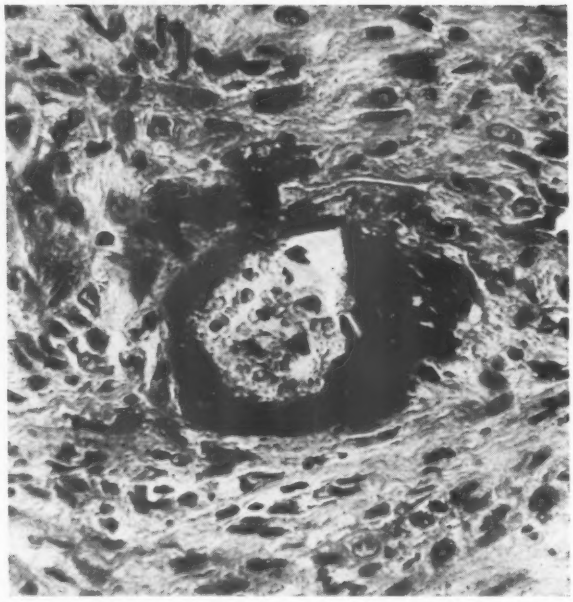

FIG. 4.—Section from the perirenal connective tissue in Case 3, showing hyalinization in a small artery. Sections stained with Masson's trichome, and photographed through a green filter (× 390).

At necropsy there was seen to be extreme wasting of the muscles and viscera. Moderate hydrocephalus was found, and generalized miliary tuberculosis. The heart weighed 140 g. (normal 115 g.); there was left ventricular hypertrophy, the muscle of the left ventricle being

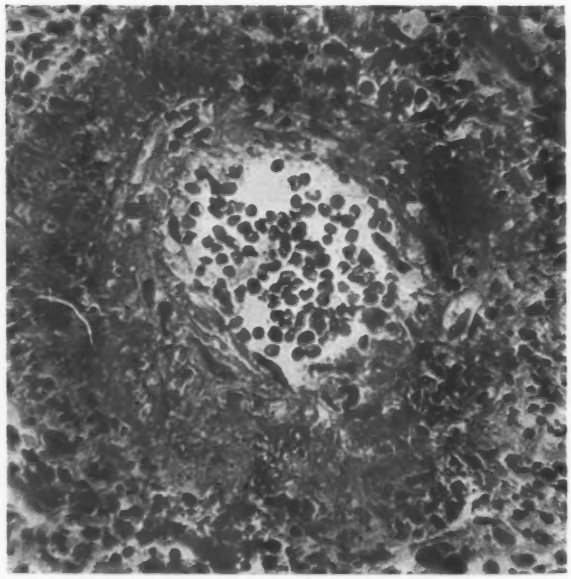

FIG. 5.—A small artery in the liver from Case 3 showing hyalinization and degeneration of the muscle (haemotoxylin and eosin × 390).

13 mm. thick. No abnormal lesions were found in the cardiac valves, the kidneys, or any blood vessels examined.

Case 5. A boy, aged 6½ years, died 14 weeks from the onset of meningitis.

At necropsy the body was seen to be extremely wasted. Old and recent miliary tuberculosis was present. The brain showed mild internal hydrocephalus with some dilatation of the fourth ventricle. The heart weighed 110 g. (normal 97 g.); the valves and vessels were normal. The left ventricle appeared to be concentrically thickened, the muscle measuring 13-14 mm. The right ventricle measured 3-4 mm. No histological change was found in the visceral vessels, but the cerebral vessels showed the usual tuberculous endarteritis.

Case 6. A girl, aged 2 years 11 months, had symptoms of meningitis two months before treatment was started. After an apparent initially good response to streptomycin, her condition deteriorated and she died four months from the onset of the disease after severe convulsions which were only controlled by very heavy sedation.

At necropsy extensive hydrocephalus was seen, the thickness of the brain being 1-2·5 cm. There was thinning of the base of the fourth ventricle. There was no visible generalized tuberculosis. The heart (Fig. 6) weighed 122 g. (normal 61 g.). The left ventricle showed considerable hypertrophy, measuring 13-17 mm. thick. No abnormalities were found in the valves or great vessels. The liver weighed 467 g. (normal 426 g.).

Comment on Cases

All the bodies were extremely wasted when they came to necropsy, and the weights of the hearts are not easy to interpret. The heart weights in several cases were higher than the average normal, but in all cases they were disproportionately high when compared with the diminished weight of the other organs. The change in the relative thickness of the left ventricle is best seen when compared with a normal heart of the same age (Fig. 6).

No anatomical abnormalities were found in the hearts or great vessels, and the heart muscle and coronary vessels were normal on microscopy. The changes in the left ventricles suggest a work hypertrophy. The most likely cause for the muscular hypertrophy is in association with a rise in systemic blood pressure, probably due to an increase in peripheral vascular tone.

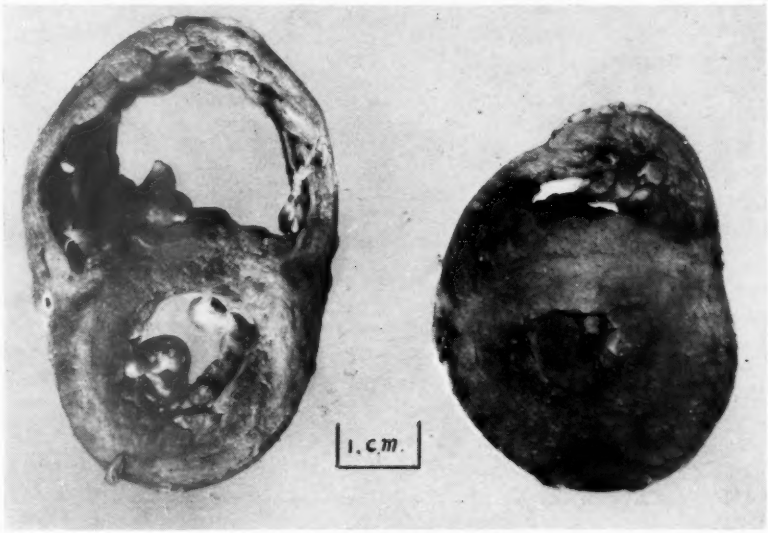

FIG. 6.—Transverse section of the ventricle of the heart in Case 6; also a section of a normal child's heart for comparison.

Discussion

Since the observation by Naunyn and Schreiber (1881) that hypertension could be produced in animals by the injection of fluid under pressure into the cisterna magna, and by Cushing (1902 and 1903) that hypertension could be produced by raising the intracranial pressure, there have been a large number of studies of central nervous hypertension.

Cushing showed that the hypertension was obviated by the injection of cocaine, and Forster (1943) found that the site of the reaction was situated in the medulla, and that decerebration tended to enhance the hypertensive response to increased intracranial pressure.

The hypertension response was shown by Grimson, Wilson, and Phemister (1937) to require the presence of an intact sympathetic nervous pathway. Thomas (1941) showed that in dogs the response took place in the absence of the kidney, and Grimson (1940), after renal denervation. Griffith and Roberts (1938) showed that the hypertension was also independent of the adrenals or adrenalin. Cushing had noticed that the major symptoms of the cerebral compression occurred with 'an approaching capillary anaemia of the medulla,' and Nowak and Walker (1939) found that progressive ligation of various cerebral arteries resulted in chronic hypertension. Raab (1931) has shown that the hypertension may be produced by perfusing the vasomotor centres with lactic acid but not with alkali.

The method frequently used to produce persistent hypertension in animals has been to promote a chronic meningeal reaction by the injection of kaolin into the basal cisterns (Hamperl and Heller, 1934; Griffith, Jeffers, and Lindauer, 1935). Hamperl and Heller in

histological studies of their hypertensive animals found foreign body reaction and granulation tissue around the medulla, blocking the foramina of Magendie and Luschka, and producing hydrocephalus. There was also perivascular 'round celled' infiltration. No abnormal vascular changes were found in the rest of the body.

I have been unable to find published records of hypertension produced by bacterial meningitis, but the association of hypertension with cerebral tumours involving the posterior fossa with bulbar types of poliomyelitis and pontine lesions are recognized. Meyer (1941) reported hypertension in four of five cases of tumour of the posterior fossa, and Ask-Upmark (1935) in an extensive review of cerebral lesions records an incidence of hypertension in 9% of cases of posterior fossa tumour, compared with 1·3% in those of anterior fossa tumour. The hypertension appeared to be independent of the cytology or particular area involved by the tumour. Three cases have been reported by Salus (1932), and one by Nordmann and Müller (1932) in which hypertension occurred associated with bulbar poliomyelitis. Serial section of the medulla showed extensive degeneration in the substantia reticularis grisea in which the blood pressure regulating centre is postulated.

Children with tuberculous meningitis now live longer than previously but frequently develop extensive internal hydrocephalus and inflammatory changes in the blood vessels of the brain. The cerebral lesions in these children are known to be chiefly due to vascular damage and ischaemia. This, combined with the rise in the intracranial pressure due to blockage of the cerebrospinal fluid, seems to produce the conditions which in experimental animals cause hypertension, and it is reasonable to expect minor degrees of hypertension to occur fairly frequently in these children.

In the rats in which hypertension was produced by kaolin Griffiths and Roberts (1938) noted that recovery from hypertension tended to occur in one to three months from the time of injection, and this suggests that the hypertension in children similarly would not be permanent.

It has not until now been part of the routine care of tuberculous meningitis in this hospital to take careful and regular blood pressure recordings, and for this reason no clinical evidence concerning blood pressure has been reported here. The necropsy findings in these cases do not, however, necessarily indicate that the blood pressure was raised to high levels, for, as Goldring and Chasis (1944) stress, the level of the blood pressure is not directly related to the severity of the vascular change, and it is possible that very small rises in the diastolic blood pressure may have produced the left ventricular hypertrophy. It is possible, however, that careful recordings of the blood pressure in tuberculous meningitis may serve as a guide to the presence of incipient medullary ischaemia.

Summary

The morbid anatomical finding of concentric hypertrophy of the left ventricle in six of a series of 16 children dying from tuberculous meningitis treated with streptomycin are reported.

It is suggested that the hypertrophy is due to hypertension of cerebral origin and is similar to the hypertension produced in animals by medullary ischaemia and by the cisternal injection of kaolin.

It is a pleasure to acknowledge the interest and helpful criticism of Dr. E. H. Harding. The photographs were taken by Mr. A. F. Taylor.

REFERENCES

Ask-Upmark, E. (1935). *Acta psychiat., Kbh.*, Suppl. 6.
Cushing, H. (1902). *Amer. J. med. Sci.*, **124,** 375.
—— (1903). *Ibid.*, **125,** 1017.
Forster, F. M. (1943). *Amer. J. Physiol.*, **139,** 347.
Goldring, W., and Chasis, H. (1944). 'Hypertension and Hypertensive Disease.' New York.
Coppoletta, J. M., and Wolbach, S. B. (1933). *Amer. J. Path.*, **9,** 55.
Griffith, J. Q., Jeffers, W. A., and Lindauer, M. A. (1935). *Amer. J. Physiol.*, **113,** 285.
——, and Roberts, E. (1938). *Ibid.*, **124,** 86.
Grimson, K. S. (1940). *Proc. Soc. exp. Biol., N.Y.*, **44,** 219.
——, Wilson, H., and Phemister, D. B. (1937). *Ann. Surg.*, **106,** 801.
Hamperl, H., and Heller, H. (1934). *Arch. exp. Path. Pharmak.*, **174,** 517.
Meyer, B. C. (1941). *Arch. Neurol. Psychiat.*, **45,** 468.
Naunyn, B., and Schreiber, J. (1881). *Arch. exp. Path. Pharmak.*, **14,** 1.
Nordmann, M., and Müller, O. (1932). *Klin. Wschr.*, **11,** 1371.
Nowak, S. J. G., and Walker, I. J. (1939). *New Engl. J. Med.*, **220,** 269.
Raab, W. (1931). *Arch. intern. Med.*, **47,** 727.
Salus, F. (1932). *Klin. Wschr.*, **11,** 1542.
Thomas, C. B. (1941). *Proc. Soc. exp. Biol., N.Y.*, **48,** 24.

SUBACUTE BACTERIAL ENDOCARDITIS IN A YOUNG CHILD

BY

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The incidence of subacute bacterial endocarditis in congenital heart disease is low. In the case reported below this condition was further complicated by bizarre embolic phenomena and is therefore considered worth recording.

Relationship of Congenital Heart Disease to Subacute Bacterial Endocarditis

Horder (1909) reviewed 150 cases of subacute bacterial endocarditis at all ages and found that congenital heart lesions were present in eight (5·3%). In 250 similar cases reviewed by Kelson and White (1945) there were 13 (5·2%) congenital heart lesions, and in a further 88 cases seen between 1939 and 1944 White, Mathews and Evans (1945) recorded 12 (13%), whilst Seabury (1947) put the incidence at 13 to 15% and Gartrell (1949) at 8%. Kelson (1945) reviewed the literature between 1939 and 1944 and found mention of only eight cases of congenital heart lesions—excluding patent ductus arteriosus—in which subacute bacterial endocarditis was a complication.

Gelfman and Levine (1942) analysed 34,023 necropsies performed in various American hospitals and found that of the 453 (1·33%) congenital heart lesions, subacute bacterial endocarditis occurred in 35 (6·6%).

Incidence of Subacute Bacterial Endocarditis in Children

In cases where no congenital heart lesions are found, the incidence of subacute bacterial endocarditis is very low. Schlesinger (1928) in a review of necropsies performed between 1862 and 1927 at The Hospital for Sick Children, Great Ormond Street, found only 10 cases of this disease, and in a further 3,044 necropsies performed at the same hospital between 1928 and 1946 (Schlesinger and MacCarthy, 1949) there were only nine true examples of subacute bacterial endocarditis. From 1946 until December, 1949, there had been no further necropsies on this condition at The Hospital for Sick Children (Bodian, personal communication).

Age Incidence. The age incidence is variable, but the disease is rare in the very young. Of Horder's cases, only two were under 5, the younger being 2½ years. A similar age incidence was found by Kelson and White, Libman and Friedberg (1941), Schlesinger, Seabury, and Gelfman and Levine. The last recorded subacute bacterial endocarditis complicating a patent interventricular septal defect in a 3-weeks-old girl.

Involvement of Aortic Valves

In children and adults the aortic valves are commonly affected. In Horder's series, which included the disease superimposed on rheumatic heart lesions, 22 (14·6%) of his cases showed the aortic cusps only to be affected.

Abbott (1932) emphasized that bicuspid aortic valves in particular were very susceptible to this affection, and, as in the case reported below, rarely are the valves of equal size. White found bicuspid aortic valves in two of his cases with congenital heart lesions, and Gelfman and Levine noted that the case incidence of bicuspid aortic valves in the general necropsy population was 1·5%, all in cases over 2 years of age, and that in 17·4% of these bacterial endocarditis was present.

Taussig (1947) considers that subacute bacterial endocarditis is the most frequent cause of death in aortic and subaortic stenosis.

Incipient Onset

In their review, Kelson and White stressed the mild way in which the disease may begin both in children and adults, common symptoms being listlessness, misery, and 'going off the legs'. In such cases, the predisposing cause is unknown, but respiratory infection, especially 'grippe' and the common cold, and of course dental extractions, are important aetiological factors. They also mention that 'in persons with pre-existing valvular or congenital heart disease, *streptococci viridans* usually disappear from the blood quickly and without harmful effect, but they may implant in crevices of

the endocardium, become surrounded with platelets and fibrin, and establish bacterial endocarditis.'

Case Report

A boy, aged 2 years and 10 months, was originally referred to hospital in September, 1948, on account of a cardiac murmur found at a routine examination.

His mother's pregnancy had been normal, and his birth weight was 7 lb. 11 oz. Apart from having been slightly underweight, he had been perfectly well and was then 31 lb., a normal weight for his age. Clinical examination at this time revealed a normal-sized heart, a thrill at the base, and a harsh systolic murmur maximal over the centre of the praecordium conducted up to the neck. A provisional diagnosis of aortic stenosis was made.

Radiological examination of the chest showed the general contour of the heart to be within normal limits.

On February 3, 1949, he returned to hospital because two months previously (i.e. at the age of 3 years 1 month) he had become listless, miserable, and pale, had lost his appetite, perspired unduly, and ' went off his legs '.

On admission to the Belgrave Hospital for Children he was very pale, sweating and lethargic. His temperature rose daily from 98·4° F. in the morning to 103·4° F. at night. Early finger clubbing was present. The heart was now slightly enlarged judged by the apex beat, but otherwise cardiac signs were as noted in September, 1948. The spleen was palpable, but there was no evidence of emboli.

Results of investigations at this time were: haemoglobin 46% (7·18 g., Haden); W.B.C.s 14,600 per c.mm. (neutrophils 73%, lymphocytes 18%, monocytes 9%); B.S.R. 55 mm. in 1 hour (Wintrobe). A radiograph of the chest showed generalized cardiac enlargement without changes in the lung fields. The tuberculin jelly test was negative. *Streptococcus viridans* was grown from a blood culture taken on February 9. Urine was normal with no microscopic haematuria.

TREATMENT. On February 10 intramuscular injections of penicillin, 200,000 units four-hourly, were begun, and after two weeks the child's temperature settled, but rose again after a further 12 days, and so on February 22 the dosage was raised to 500,000 units four-hourly. Fourteen days after the increased dose, his temperature became normal and remained so for seven weeks. On March 11 a blood transfusion of 180 ml. of packed cells was given which raised his haemoglobin to 70%, at which it remained. On March 30 the penicillin dosage was reduced to 500,000 units q.d.s. The total dosage of penicillin was 158 million units.

Few embolic episodes were noticed. Occasionally he complained of pain in the region of his spleen, which was tender, though no rub was ever heard. His urine was examined microscopically on frequent occasions, but only once were numerous red cells found. Blood culture was repeated on February 24 and on four subsequent occasions, and was consistently sterile.

Throughout this time the murmurs as originally noted had not altered, though two months after his admission he was found to have a collapsing pulse, a slight clinical cardiac enlargement and an aortic diastolic murmur, which, a month later, had disappeared. On April 1, a week after this murmur was first noted, he developed pain and loss of movement of his right wrist joint and elbow, but 14 days later these symptoms had disappeared. On April 11 his penicillin was stopped, but 12 days later his temperature rose, and beginning April 26 the penicillin, 500,000 units q.d.s., was given for a further six days, once again rendering him afebrile.

A week later the child again became unwell and again an aortic diastolic murmur was noted. That same night he had a sudden onset of pain in the right thigh, and although pulsation could easily be felt in the right femoral artery, it was absent in the corresponding popliteal and dorsalis pedis vessels. His right leg was discoloured and colder than the left, though it returned to normal within 48 hours.

Seventeen days later, on May 25, a further embolic episode was noted by one of the nurses, who reported that she was unable to feel his right radial pulse. This was confirmed, and in addition pulsation was found to be absent in the brachial artery. Despite these phenomena, his general condition improved after a further blood transfusion on June 1 of 200 ml. of packed cells.

The child became very lively, ran about the ward without a limp, and showed no disability in his right arm. He was given another transfusion of 300 ml. of packed cells on July 1, raising his haemoglobin to 84% (13·1 g.). His heart now showed definite clinical enlargement to the left, and on auscultation an aortic systolic and diastolic murmur was heard, the systolic murmur conducted to the mitral area. With these findings he was discharged home after 5½ months in hospital.

Three weeks later he was readmitted because he had been unwell and vomited for 48 hours.

Examination then revealed a very dyspnoeic, restless, pale child with a temperature of 98°, and pulse 135 a minute. His heart was clinically grossly enlarged, confirmed by radiographs which showed a certain amount of vascular congestion in the lungs, although at this time there were no signs of right-sided heart failure. Blood tests gave: haemoglobin 58% (9·05 g. %); R.B.C.s 2,800,000 per c.mm.; colour index 1·03; W.B.C.s 9,240 per c.mm. (neutrophils 56%, lymphocytes 42%, large mononuclears 2%).

The child remained very ill, and the next day developed an irregular pulse, distended neck veins, and an enlarged liver. He died the same day, nine months after the onset of illness.

Necropsy. Necropsy was performed by Dr. B. S. Cardell, King's College Hospital Medical School, and his report follows.

The body was that of a thin male child showing slight cyanosis of the face and extremities. There was no oedema or abnormal pigmentation.

The heart was much enlarged, weighing 235 g. (normal 60 g.) with marked left ventricular hypertrophy, the myocardium attaining a maximum thickness of 1·2 cm. The aortic valve was bicuspid, the two cusps being of unequal size. A moderate degree of aortic stenosis was produced by the rigid and distorted cusps, from which

large calcareous vegetations projected. The left ventricular endocardium was roughened immediately below the left aortic cusp. The aortic valve ring itself was not stenosed, measuring 6·1 cm. in circumference. The ascending aorta was slightly dilated (5·9 cm. in circumference), and on the posterior wall 3 cm. above the valve ring there was a roughly circular atheromatous plaque 2 cm. in diameter (Figs. 1 and 2).

The lungs (left 195 g., right 275 g.) were congested and poorly aerated, with no evidence of infarction. The liver was congested (550 g.). The spleen was slightly enlarged (75 g.) and showed one small old infarct. There were two small, old infarcts in the left kidney and one in the right. The right femoral artery was obliterated 5 cm. above the knee, being represented for a distance of 0·5 cm. by a fibrous cord and in the lower axilla the right brachial artery was similarly obliterated.

Sections of the kidneys and myocardium revealed no evidence of active lesions.

FIG. 1.—Enlarged heart with marked left ventricular hypertrophy.

Discussion

Several interesting features of subacute bacterial endocarditis are illustrated by this case and by the literature.

Rarity in Childhood. Subacute bacterial endocarditis is rare in childhood and especially in such a young child as this case.

Incidence in Heart Lesions. Subacute bacterial endocarditis occurs in approximately 5-15% of congenital heart lesions and is the most frequent cause of death in aortic and subaortic stenosis. Bicuspid aortic valves are especially susceptible to this disease.

Embolic Phenomena. Wagner (1948) mentions that cerebral embolism is an occasional unpredictable cause of death during prolonged therapy, and that emboli are responsible for infarcts in other organs.

Williams and Nelson (1949) found emboli which were clinically renal, pulmonary or cerebral, but no necropsies were done on these cases. In three of their 12 cases treated with penicillin, petechiae and/or embolic phemonena were noted several days or weeks after blood cultures became sterile.

FIG. 2.—Large vegetations projecting from bicuspid aortic valve. Circular atheromatous plaque in ascending aorta.

In the 165 patients reviewed by Seabury, embolism occurred in 57% of all cases, both in rheumatic and congenital heart lesions.

The arrest of the disease after vast doses of penicillin is liable to lull one into a false sense of security, and any vegetations formed, although sterile, are still very friable and therefore liable to break off from their attachment. In this child's arm and leg there was an efficient collateral circulation following complete occlusion of the main arteries by emboli.

Residual Cardiac Damage. The increase in residual cardiac damage after apparent cure of the infection has been emphasized by Morgan Jones, Herring, Langley, and Oleesky (1947). These authors also noted that the duration of the disease before the beginning of treatment was the most important factor in prognosis.

From evidence found at necropsy in this case, it would seem that the stenosis increased as the vegetations fibrosed, eventually causing heart failure.

Thrill and Meyer (1947) mention that in healed endocarditis the vegetations undergo fibrous organization.

Results of Penicillin Therapy. Christie (1948) summarized the results of treatment of this condition with penicillin in 269 patients at 14 centres in Great Britain. He noted that of the 94 patients in whom the infection was apparently controlled, but who subsequently died, 45 died of heart failure, and this was a major cause of death in a further 14. Nine died as a result of emboli.

The heart valves were examined in 47 cases, in 39 of which infection appeared controlled. In this group, however, presumed living organisms were seen in the heart valves of 13; organisms of uncertain viability in four; and apparently dead organisms in nine. In the remaining eight patients, infection was not clinically controlled, though in two no organisms could be demonstrated.

These patients were further followed up (Christie, 1949) for another two years, and, in addition 139 new cases were reported. The factors mentioned in the first report as affecting the cause of death were confirmed, but the original suggested dosage of 500,000 units of penicillin daily for one month was revised to a dose of 2,000,000 units a day for four to six weeks.

Seabury's review covers a period before and after the advent of penicillin. Of 12 patients treated with penicillin, seven (58%) had probably been cured (i.e., these were well after a minimum period of one year). He thought that the reports available at the time indicated that penicillin could be expected to be efficacious in from 65 to 70% of cases of subacute bacterial endocarditis.

Wagner analysed 521 cases in the literature treated with penicillin. Clinical arrest occurred in 371 (71·3%) and in an additional 95 (18·2%) a 'cure' was produced in the hospital, but the disease recurred and the patients died within three to four months. The remaining 55 (10·5%) were complete clinical failures.

Summary

A case of congenital aortic stenosis in which subacute bacterial endocarditis occurred at the early age of 3 years is recorded. Although apparently cured of the infection, the child suffered embolic occlusion of the brachial and femoral arteries. Seventeen days after discharge from hospital he died of heart failure due to an increasing aortic stenosis, the result of fibrosis of vegetations on the aortic valve. The literature is discussed.

I wish to thank Dr. Mary Wilmers, under whose care this child was admitted, for very helpful criticism and for permission to publish, and Prof. H. A. Magnus for permission to describe the necropsy. Dr. N. F. Elliott Burrows kindly corrected the draft manuscript for me.

References

Abbott, M. E. (1932). 'Contributions to the Medical Sciences in Honour of Dr. Emanuel Libman,' vol. 1, p. 1. New York.
Christie, R. V. (1948). *Brit. med. J.*, **1**, 1.
—— (1949). *Ibid.*, **2**, 950.
Gartrell, E. F. (1949). *Med. J. Aust.*, **1**, 353.
Gelfman, R., and Levine, S. A. (1942). *Amer. J. med. Sci.*, **204**, 324.
Horder, T. J. (1909). *Quart. J. Med.*, **2**, 289.
Jones, A. Morgan, Herring, R., Langley, F. A., and Oleesky, S. (1947). *Brit. Heart J.*, **9**, 38.
Kelson, S. R. (1945). *Ann. intern. Med.*, **22**, 75.
——, and White, P. D. (1945). *Ibid.*, **22**, 40.
Libman, E., and Friedberg, C. K. (1941). 'Subacute Bacterial Endocarditis.' New York.
Seabury, J. H. (1947). *Arch. intern. Med.*, **79**, 1.
Schlesinger, B. E. (1928). *Brit. J. Child. Dis.*, **25**, 33.
——, and MacCarthy, D. (1949). In Garrod, Batten, and Thursfield's 'Diseases of Children,' vol. 2. London.
Taussig, H. B. (1947). 'Congenital Malformations of the Heart.' New York.
Thrill, C., and Meyer, O. (1947). *Amer. J. Med. Sci.*, **213**, 300.
Wagner, B. M. (1948). *Ibid.*, **215**, 84.
White, P. D., Mathews, M. W., and Evans, E. (1945). *Ann. intern. Med.*, **22**, 61.
Williams, R. K., and Nelson, K. (1949). *Va. med. Mon.*, **76**, 589.

A CONGENITAL FACTOR IN BRONCHIECTASIS

BY

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The majority of sufferers from bronchiectasis state that their symptoms began in childhood. There is good evidence for believing that the disease is usually of acquired origin, but in a few cases the presence of other developmental anomalies favours the view that there may also be a congenital factor.

Sauerbruch (1934) considered bronchiectasis was due to mechanical crowding, particularly of the left bronchial tree, during development and that some dilatation of middle-sized and large bronchi was present at birth, if the crowding and stricture occurred in late foetal life. Bronchial infection, secondary to measles, scarlet fever, pneumonia or pertussis, superimposed on the previous developmental condition, constituted bronchiectasis as seen clinically. He maintained that the absence of adhesions about bronchiectatic lobes, the normal appearance of the surrounding parenchyma, the absence of a history of pneumonia, and the irregularity of the layers of the bronchial wall were in favour of a congenital origin in this disease. Engel (1947) suggested the possibility of a congenital weakness of the bronchial walls in bronchiectasis in childhood. In Engel's view this inborn constitutional weakness is probably present in the condition known as congenital laryngeal stridor, and is also a factor in pulmonary collapse because of the individual susceptibility in the latter, which cannot be related to the viscosity of bronchial mucus.

Kartagener (1933) has deduced that bronchiectasis is mainly congenital from his observation that an extraordinary number of cases of complete transposition of the viscera also suffer from bronchiectasis. He quoted the figure of 25%; Adams and Churchill (1937) found a similar proportion, but Olsen (1943) gave a lower figure, 16·5%.

The frequency rate of occurrence of situs inversus totalis in the general population is:

At necropsy.....1 in 5,000 (Kartagener, 1933).
Clinically.....1 in 10,099 (Adams and Churchill, 1937). Massachusetts.
1 in 19,500 (Cockayne, 1938). England.
By radiology....1 in 1,400 (Le Wald, 1925).

The appearance then of an uncommon condition, such as bronchiectasis, in 25% of cases with a rare anomaly like complete situs inversus suggests that there must be some definite relationship. Adams and Churchill are of the opinion that there are two types of individuals with transposition of viscera, perfectly normal mutants and monsters in whom other stigmata of malformation can be found, of which bronchiectasis is one. Olsen (1943), in 85 cases of dextrocardia, found 14 with bronchiectasis and 11 of the 85 patients had other congenital defects. Eliman (1935) described a case of situs inversus totalis, in which there was congenital pulmonary stenosis and physical signs of a cavity at the apex of the left lung. Certainly in the case of partial situs inversus congenital malformations are very common, and Maude Abbott (1936) found congenital heart disease in almost all her cases. Kartagener and Horlacher (1935) reported a case in the literature with partial situs inversus and bronchiectasis.

Cockayne (1938) from an extensive study of the literature and his own cases produced strong evidence that transposition of the viscera was a rare recessive character. If situs inversus totalis is a dominant or a recessive character it should affect both members of a pair of monozygotic twins or neither. Araki (1935) has recorded transposition in a pair of monozygotic twins. If heterozygotes for a recessive character marry there should be a proportion of one affected to three normal children, and in published cases the ratio works out at 1 to 3·1. The proportion of consanguineous marriages should be high. Cockayne found that there were 11% of first cousin marriages in the cases he studied.

A hereditary or familial influence has seldom been found in bronchiectasis, though Wiese (1927) noted that it was usually the younger child in a family who was affected, and Hinshaw and Schmidt (1944) and Pastore and Olsen (1941) recorded similar bronchiectasis in identical twins. Torgersen (1946) found transposition of viscera in three of the five children of one Norwegian family. All three had a

productive cough which suggested bronchiectasis López Areal (1944) reported a family in which the parents were first cousins and three of their 11 children had transposition of the viscera and bronchiectasis.

In the literature on Kartagener's syndrome, the type of bronchiectasis recorded is usually tubular or varicose, instead of the cystic variety generally regarded as congenital. Clagett (1942) recorded bronchiectasis in 2 to 4% of routine necropsies; clinically, Kartagener (1933) found it in 0·25% and Adams and Churchill (1937) in 0·3% of cases. Nüssel and Helbach (1934) argued that the deduction of an inherent predisposition to bronchiectasis could not as yet be made because of the unreliable preceding history in most cases of Kartagener's syndrome. This syndrome, as described by Kartagener, includes nasal sinusitis, but it is improbable that there is a congenital liability to sinusitis and the bronchiectasis is secondary to it, because four of Olsen's cases with dextrocardia and bronchiectasis did not have nasal sinusitis and a further four cases had dextrocardia and sinusitis without bronchiectasis. On the other hand, Richards (1944) noted congenital absence of the frontal sinuses in bronchiectasis associated with transposition of viscera, and Andrews (1949) reported a case with small frontal sinuses, poorly developed ethmoid labyrinths and absence of sphenoidal sinuses and mastoid air cells.

The following three cases are typical examples of complete transposition of the viscera associated with bronchiectasis.

Case Reports

Case 1. This girl was first seen when 6½ years old because of a cough, anorexia, and poor weight gain for three years. In the past she had pertussis, aged 2 years; measles aged 2½ years; tonsils and adenoids removed aged 5 years. The parents were not blood relations and other siblings were normal. On examination the child was seen to be pale and thin. She had a nasal discharge, and a persistent productive cough with yellow sputum. There was an impaired percussion note in the chest, diminished air entry, and crepitations at the right base. The heart apex lay on the right side in the fifth space ½ in. outside the nipple line; a systolic murmur at the apex was heard. The liver was palpable below the left costal margin. The Mantoux (1/100) reaction was negative. A radiograph of the chest showed transposition of the heart and abdominal viscera, and the maxillary antra that both were opaque. An ECG gave inversion of all primary waves in lead I, with R3 larger than R2. A right bronchogram showed varicose bronchiectasis in the right lingula and the right lower lobe bronchi (Fig. 1); the left bronchi were normal. The arrangement of the bronchial tree was a mirror image of the normal.

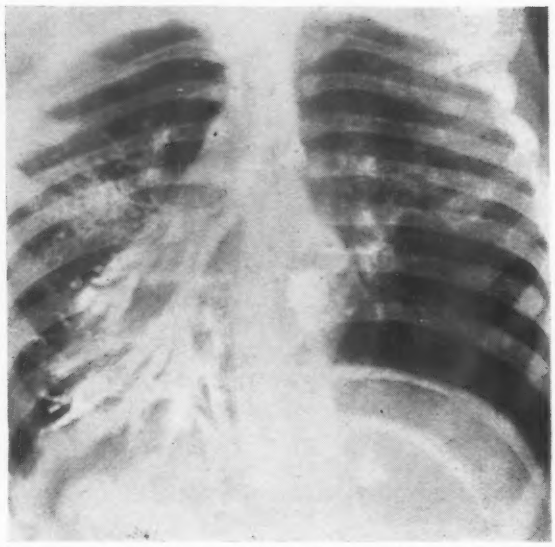


FIG. 1.—Varicose bronchietasis in the right lingula bronchi and right lower lobe bronchi.

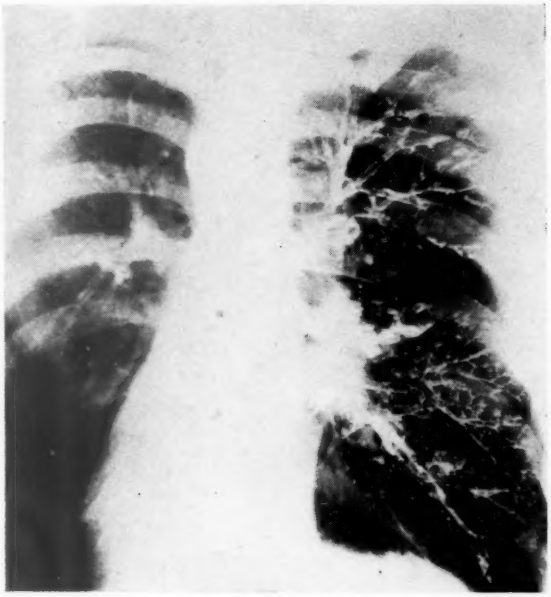
Case 2. A man, aged 37 years, had had bronchitis all his life, with a cough productive of sputum. He had had nasal catarrh for 21 years, and slight retrosternal pain occasionally. He has spasms of coughing and feels that his chest is compressed if he lies on his right side when in bed. His cough is worse on rising, though he has it all the time, and often wheezes. His sputum is yellowish, never offensive, and more is brought up in wet weather, or when he bends down. He has had no haemoptyses.

He gave a history of pneumonia at the age of 1 year on the right side, and again on the right side at 12 years. In 1925 he spent a year in the army, and again in 1941-1942 (Grade B.2), but was discharged because of his chronic bronchitis.

On examination he was seen to be a pale, rather thin man, with slightly clubbed fingers. The trachea was central. The apex beat was heard in the right fifth interspace. Liver dullness was perceived on the left. The percussion note was impaired at the right base posteriorly with increased conduction of breath sounds and numerous moist rales. The physical signs were suggestive of collapse of the right lower lobe. There were moist sounds in the left midzone anteriorly and posteriorly.

A left bronchogram showed cystic bronchiectasis in the left middle lobe, and a right bronchogram bronchiectasis and partial collapse of the right lower lobe (Figs. 2 and 3). The right lingula segment showed mottled opacities and translucencies but the bronchi were not outlined.

Case 3. A girl, aged 8¾ years, had had chronic nasal catarrh, cough, and wheeziness all her life. She was four weeks premature at birth, and in her past medical history she has had pneumonia on three occasions, measles, chickenpox, mumps and a tonsillectomy. The Mantoux reactions were negative.



FIGS. 2 and 3.—Varicose bronchiectasis in some of the right lower lobe bronchi, and saccula bronchiectasis in the right lingula bronchi and left middle lobe bronchi.

The patient had two prematurely born male sibs who died in early infancy, one other brother who was killed in a road accident in early childhood, and one normal sister aged 7 years. The parents were second cousins. A first cousin of the patient also has transposition of viscera but no productive cough.

On examination she was seen to be a well built girl with chronic nasal catarrh and a cough productive of 4 oz. of sputum a day. There was moderate air entry and chest movements, and crepitations at both lung bases and a few scattered rhonchi. The fingers were not clubbed. The heart and abdominal viscera were transposed. An ECG showed the typical changes of a mirror image dextrocardia. The maxillary sinuses were opaque on radiography. Bronchography showed that the bronchial tree was a mirror image of the normal with bronchiectasis in the right lingula bronchi (Fig. 4).

It is probable that permanent pulmonary parenchyma as seen in adults develops only after birth and takes a matter of years. The development of the lung by differentiation, budding, and expansion of pulmonary anlages is usually fairly complete by about the age of puberty (Strukow, 1932; Willson, 1928, and Miller, 1934). Bronchiectasis may afflict those parts of the lungs which fail to expand after birth and remain in their foetal atelectatic state. The proper formation of alveoli does not occur in portions of atelectatic lung, so that the evacuating mechanism of an expulsive blast of air through the bronchi on expiration or coughing is not established. Secreted mucus may become infected if not removed adequately and bronchial weakening and dilatation would then occur. The centrifugal pull of negative intrapleural pressure probably has little effect on the bronchi while the infant's chest is still pliant and can be sucked in, but atmospheric pressure acting down them when they are unsupported externally by aerated alveoli can cause dilatation.

Heller (1885) and Francke (1894) attributed so-called congenital cystic disease of lungs to the saccular dilatations of small bronchi and bronchioles formed in atelectatic lung, and other writers ascribed

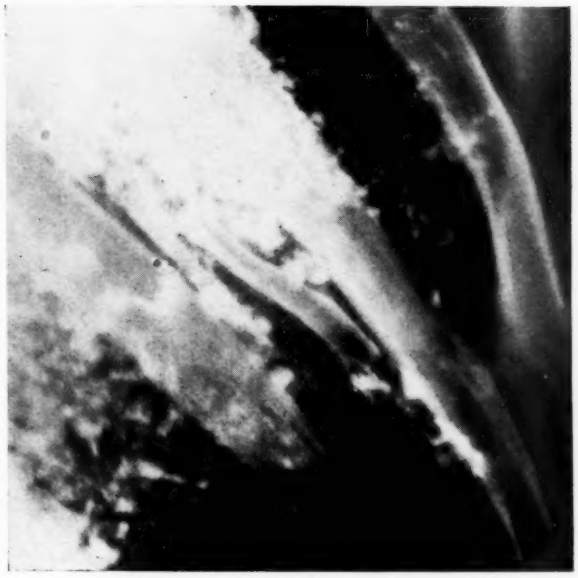


FIG. 4.—Tubular bronchiectasis affecting the upper division of the right lingula bronchi. The lower division is probably ectatic but is not adequately filled.

honeycomb cysts with cuboidal cell lining to the over-distension of the relatively few alveoli which develop in an atelectatic lobe. Engel (1947) pointed out that atelectasis persisted longer in the lower posterior peravertebral areas of the lung, particularly on the left side, and remarked that these were the usual sites for bronchiectasis. It is possible that atelectasis is particularly common in the neonate with transposition of the viscera, and that it predisposes to the development of bronchiectasis. A further case will illustrate this point.

Case Report

Case 4. This boy was sent to hospital when 5 weeks old because of a heavy cough and fever, which was thought to be due to pneumonia. The cough has persisted ever since. When 4 months old he was noticed to have dextrocardia and left upper lobe atelectasis.

The patient was the first child (birth weight 9 lb.). Pregnancy and delivery were normal.

A second child was born at full term but weighed only 4 lb. 2 oz. He suddenly died in the night aged 4 months (cause unknown). The mother and father are alive and well, and are not blood relations. One uncle was born with a deformity; he had a tag on the outer side of each hand, suggestive of a rudimentary sixth finger. One cousin was born without a hand. There is no asthma in the family.

On examination in January, 1944, when aged 7 months, the baby was seen to be well nourished. Frontal bossing was apparent, especially on the left side. He had an extra finger on each hand. The liver was on the left side, and the stomach on the right. The chest percussion note was dull with rales and tubular breath sounds over the left apex anteriorly. A radiograph confirmed the left upper lobe atelectasis and dextrocardia (Fig. 5). The Mantoux test (1/1,000) was negative.

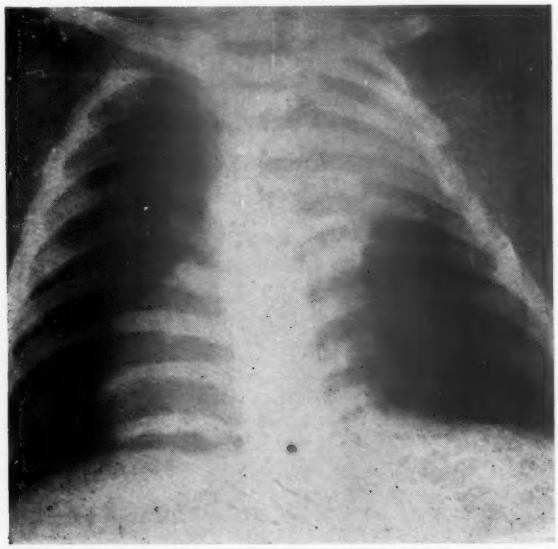


FIG. 5.—At 7 months. Atelectasis of the left upper lobe. Transposition of viscera.

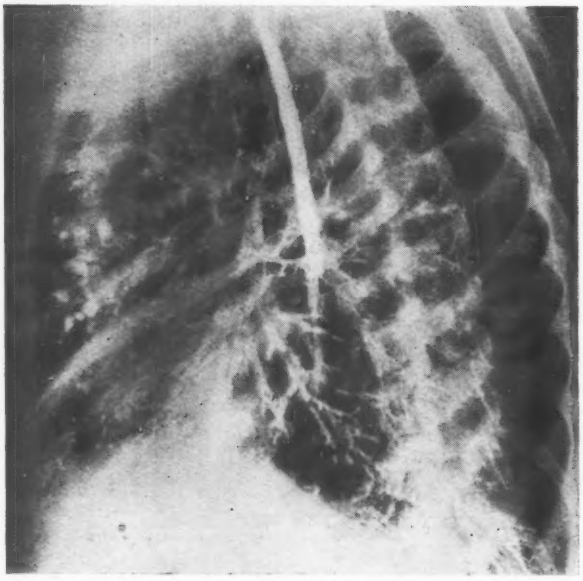


FIG. 6.—Gross saccular bronchiectasis in the pectoral segment of the left upper lobe. Less severe bronchiectasis in some of the other branches of the upper and middle lobes.

Bronchoscopy showed that the left upper lobe bronchus was smaller than normal and congested, but no obstruction was visible.

Two years later (January 16, 1946) slight cough in mornings only was reported. The chest was clear clinically. A radiograph showed some crowding of the left ribs still, and a faint opacity in the left upper lobe area.

On November 15, 1947, cough was present, and the chest showed rhonchi all over. Nasal catarrh was marked. The sinuses were radiologically opaque.

In 1948 bronchography a mirror image bronchial tree was seen. Gross saccular bronchiectasis (Fig. 6) in the pectoral segment of the left upper lobe, and to a lesser degree in some of the bronchi of the upper and middle lobe was seen. The right bronchial tree was normal.

This child had been followed from birth and it was known that he had an atelectatic left upper lobe which took 24 months before it was radiologically re-expanded. The bronchiectasis may have been due to the atelectasis and not a genetical factor. Clinically he is a case of Kartagener's syndrome.

Discussion

Our knowledge of the congenital deformities that affect the lungs is not very extensive. We know something of the anomalous position of fissures and of the distribution of bronchi from studying the anatomy of the lungs in morbid specimens and from bronchography. Vascular abnormalities are sometimes observed within the lung parenchyma and these may give a bruit on auscultation. Accessory or supernumerary lung lobes have been

recorded both in the thorax and in the abdomen; Allen (1882), Chiene (1870), and Ruge (1878) described a small accessory lung behind the left lung which derived its blood supply from an intercostal space. Cysts in the mediastinum, lined by bronchial epithelium and without a direct opening into the bronchi or trachea, have been recorded by Carlson (1943), Brown and Robbins (1944), and Allison (1947). There is little doubt that some lung cysts originate from a developmental malformation. These cysts are generally connected to bronchi though they may not open directly into one. The lining epithelium is bronchial in type and the walls may contain portions of other bronchial structures such as elastic tissue, muscle, and cartilage. Lung cysts with a wall structure characteristic of bronchial tissue have been found at necropsy in stillborn foetuses by Meyer (1859), Pappenheimer (1912), Smith (1925), and Wolman (1930).

Cystic disease of lungs has been separated in the past from bronchiectasis because the former is mainly found in young children and is characterized by solitary or multiple round cavities lined by bronchial epithelium, alongside and seldom connected to the bronchi, which themselves are not much dilated. The parenchyma about congenital cysts usually lacks the carbon pigmentation seen in normally aerated lung tissue. Bronchiectasis, on the other hand, has been regarded as a disease affecting children after infancy and adults, in whom the larger, more firm-walled bronchi are widened, thickened, and inflamed, but round cysts seldom occur. It is now known that a cystic appearance in the lung can be acquired and it is suspected that dilatation of the major bronchi may sometimes be congenital in origin.

In the vast majority of cases bronchiectasis is an acquired disease. If it is sometimes congenital it should be possible occasionally to demonstrate it in a stillborn foetus or in a neonate in whom atelectasis or infection have not occurred. Histological proof of congenital malformation is very difficult and requires positive findings such as an irregular arrangement, lack of formation, or hyperplasia of tissues which could not have arisen from post-natal hypertrophy, atrophy, collapse or inflammation. Even bronchogenic cysts found in the newborn generally lack unequivocal evidence of a developmental origin. The bronchi in bronchiectasis are generally overlaid by the alterations produced by inflammation. Hypertrophy of certain stromal layers is occasionally found, but one cannot as a rule maintain that this is hyperplasia.

As direct proof of a developmental origin of bronchiectasis is still lacking, these four cases are presented to add to the weight of circumstantial evidence slowly being accumulated that a congenital factor may be of importance in the disease.

Summary

Four cases of bronchiectasis associated with complete transposition of the viscera are described. The frequency of bronchiectasis among cases with situs inversus totalis is so much greater than in the general population as to suggest that the bronchiectasis may also be due to a developmental error.

I wish to thank Dr. B. E. Schlesinger and Dr. R. E. Bonham Carter for permission to publish this article, and Miss S. Young for her secretarial help.

References

Abbott, M. (1936). 'Atlas of Congenital Cardiac Disease,' p. 58. New York.
Adams, R., and Churchill, E. D. (1937). *J. thorac. Surg.*, **7**, 206.
Allen, W. (1882). *J. Anat. Physiol.*, **16**, 605.
Allison, P. R. (1947). *Thorax*, **2**, 176.
Andrews, C. T. (1949). *Brit. med. J.*, **2**, 1269.
Araki, B. (1935). Quoted by Cockayne.
Brown, R. K., and Robbins, L. L. (1944). *J. thorac. Surg.*, **13**, 84.
Carlson, H. A. (1943). *Ibid.*, **12**, 376.
Chiene, J. (1870). *J. Anat., Lond.*, **4**, 89.
Clagett, O. T. (1942). *Proc. Mayo Clin.*, **17**, 1.
Cockayne, E. A. (1938). *Quart. J. Med.*, **7**, 479.
Eliman, P. (1935). *Proc. roy. Soc. Med.*, **28**, 333.
Engel, S. (1947). 'The Child's Lung.' London.
Francke, W. (1894). *Dtsche. Arch. klin. Med.*, **52**, 125.
Heller, A. (1885). *Ibid.*, **36**, 189.
Hinshaw, H. C., and Schmidt, H. W. (1944). *Dis. Chest*, **10**, 115.
Kartagener, M. (1933). *Beitr. Klin. Tuberk.*, **83**, 489.
——, and Horlacher, A. (1935). *Schweiz. med. Wschr.*, **65**, 782.
LeWald, L. T. (1925). *J. Amer. med. Ass.*, **84**, 261.
López Areal, L. (1944). *Rev. clín. esp.*, **14**, 378.
Meyer, H. (1859). *Virchow's Arch.*, **16**, 78.
Miller, J. A. (1934). *J. thorac. Surg.*, **3**, 246.
Nüssel, K., and Helbach, H. (1934). *Beitr. Klin. Tuberk.*, **84**, 424.
Olsen, A. M. (1943). *Amer. Rev. Tuberc.*, **47**, 435.
Pappenheimer, A. M. (1912). *Proc. N.Y. path. Soc.*, **12**, 193.
Pastore, P. N. and Olsen, A. M. (1941). *Proc. Mayo Clin.*, **16**, 593.
Richards, W. F. (1944). *Tubercle, Lond.*, **25**, 27.
Ruge, C. (1878). *Berl. klin. Wschr.*, **15**, 401.
Sauerbruch, F. von. (1934). *Arch. klin. Chir.*, **180**, 312.
Smith, S. (1925). *Brit. med. J.*, **1**, 1005.
Strukow, A. I. (1932). *Z. Anat. Entw. Gesch.*, **98**, 348.
Torgersen, J. (1946). *Acta med. scand.*, **126**, 319.
Wiese, O. (1927). 'Die Bronchiektasien im Kindesalter.' Berlin.
Willson, H. G. (1928). *Amer. J. Anat.*, **41**, 97.
Wolman, I. J. (1930). *Bull. Ayer clin. Lab.*, **2**, No. 12, p. 49.

CONGENITAL TOXOPLASMOSIS IN AN AFRICAN CHILD

BY

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From University College, Ibadan, Nigeria

(RECEIVED FOR PUBLICATION JULY 28, 1950)

Toxoplasmosis has been reported with increasing frequency during the last decade, and the various manifestations of the human disease, with particular reference to congenital toxoplasmosis, have recently been summarized by Hutchison (1949), and Wyllie, Fisher, and Cathie (1949). All the cases thus far have been reported from America or Europe, and the case of congenital toxoplasmosis described here is the first from Africa.

Case Report

A Yoruba boy, aged about 3 years, was brought to the Adeoyo Hospital, Ibadan, W. Nigeria, on February 3, 1950. The father complained that the child had diarrhoea, having his bowels open five times each day. Blood and mucus were present in the stools. Investigation showed this to be due to bacillary dysentery, which responded rapidly to oral phthalylsulphathiazole.

Also, it was noticed that the child had an enormous head and further investigations were undertaken to discover the cause.

The child was born at home. There was no history of any difficulty during labour. No illness had occurred during the neonatal period or infancy, save for an occasional attack of 'fever' or diarrhoea. The first teeth had appeared at 9 months. The child walked at about 18 months, and was able to speak with simple sentences at about 2 years. (These figures are only approximate and could not be elaborated further.) No history of fits or paralyses or illness with unconsciousness was obtained.

The mother admitted of no history of any illness. She had had no other children and no miscarriages. Examination showed no abnormality. (The mother was very suspicious of the interest shown in her child and was convinced that a *juju* was being put on him. She therefore very likely withheld important facts.)

The parents had observed that the child's head was large a few months after birth. It had remained so ever since. They could not say whether it had increased markedly at any particular period, but were certain that there had been no increase in size in the previous six months.

Examination showed a well-nourished, pot-bellied boy (Fig. 1). He was 77·5 cm. tall and weighed 23 kg. The spleen was palpable (two finger breadths) and the liver edge could just be felt, but splenomegaly and hepatomegaly can be regarded as normal in a hyperendemic malarial town such as Ibadan. An occasional rhoncus could be heard in the chest. The apex beat was difficult to locate, but could be felt in the anterior axillary line.

The skull was greatly enlarged and box-shaped (Figs. 2 and 3). The circumference of the skull measured 60 cm.

FIG. 1.—The child with congenital toxoplasmosis.

The anterior fontanelle was widely open (about 2·5 cm. long by 1·5 cm. wide), and the sutures closed. There was no evidence of mental deficiency, cranial nerve palsy, visual disturbance, or paralysis. There were no clinical signs of rickets.

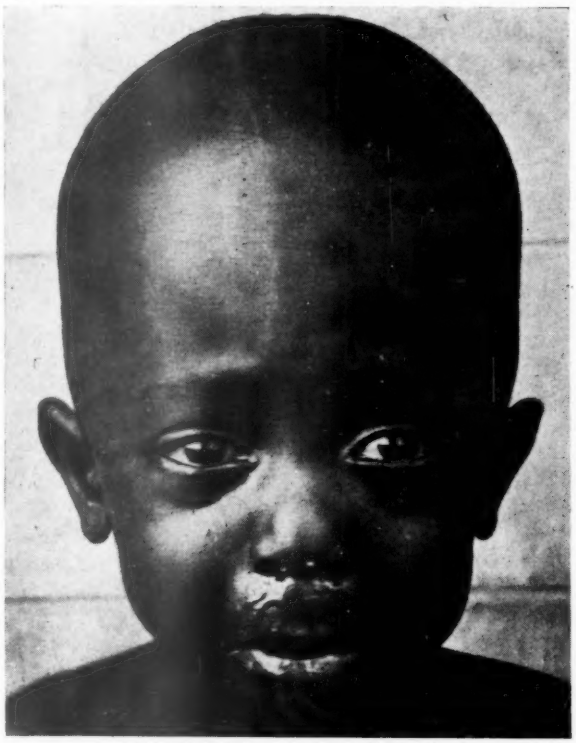

FIG. 2.—Front view of head.

Investigations. A blood count gave Hb. 73%; red blood count, 4,320,000 per c.mm.; C.I., 0·8; white blood count, 13,600 per c.mm. (polymorphs 43%, metamyelocytes 11%, lymphocytes 46%).

The tuberculin patch test was negative at two, four, and six days.

FIG. 3.—Lateral view of head.

Blood films taken on six occasions showed no malarial parasites.

Kahn tests were negative in both mother and child.

Stools were examined on six occasions, and ova of *Ascaris* only were found.

A radiograph of the wrists showed no rickets.

A lateral radiograph of the skull showed widely scattered areas of calcification, mainly of pin head size. Many were aggregated in small clusters. (Fig. 4 shows the distribution of the calcification.)

A radiograph of the chest showed a considerable degree of cardiac enlargement.

Lumbar puncture and air encephalograms were refused by the parents.

Dr. A. Dark reported that there was no abnormality in either eye, except that the right disc was hyperaemic. The lens and vitreous were quite normal. Both maculae were normal.

Serum from both the mother and the child was sent to Dr. Sven Gard, of the Statens Bakteriologiska Laboratorium, Stockholm, who reported:

'The sera from the mother and the child have been tested according to Sabin and Feldman (1948) with

FIG. 4.—Diagram of radiograph of skull showing distribution of intracranial calcification.

positive results. The mother's serum titred 1:50, that of the child 1:2,000. These findings are strongly indicative of a diagnosis of congenital toxoplasmosis in the child. According to our experience from Swedish material a positive dye-test in children below the age of 10 years is never observed except in connexion with stigmata of a toxoplasmic nature. The titre value of the mother is well compatible with the assumption of an active toxoplasmosis—with or without clinical manifestations—three years ago. Titres usually rise to 1:1,000 or higher in the active stage of infection. In cases without complications a significant decrease is observed after about three months and a level of 1:50 can be attained within a year after the onset of infection.'

A further report (May 6, 1950) stated:

'A complement-fixation test has been carried out on the sera of the mother and child. Both gave positive results, that of the mother having a titre 1:4. On account of lack

of serum, no complete titration of the child's serum was made. However, the highest dilution (1:8) tested gave a complete inhibition. These results are in good agreement with those of the previous test.'

Serum from both the mother and the child was sent to Dr. A. Macdonald, of the University of Liverpool, who reported:

'Both samples give positive complement-fixation tests with toxoplasma egg antigen. The titres were: mother 1:20 and child 1:30. The results of the dye-test and of the egg neutralization test were also positive.'

Summary

The main features of the reported case are (1) macrocephaly, possibly due to hydrocephalus, (2) radiological evidence of intracranial calcification, (3) cardiac enlargement, and (4) positive serological tests for toxoplasmosis from both the mother and the child. A diagnosis of congenital toxoplasmosis was made. It seemed probable that the infection had become either quiescent or healed.

This is the first case of congenital toxoplasmosis to be reported from Africa, all previous cases having been recorded in America or Europe.

I should like to thank Professor A. Brown, Department of Medicine, University College, Ibadan, for permission to publish this article.

My thanks are especially due to Dr. Sven Gard and Dr. A. Macdonald for carrying out the serological tests, and to Dr. A. Dark for the ophthalmic opinion.

References

Hutchison, J. H. (1949). *Archives of Disease in Childhood*, **24**, 303.

Sabin, A. B., and Feldman, H. A. (1948). *Science*, **108**, 660.

Wyllie, W. G., Fisher, H. J. W., and Cathie, I. A. B. (1949). *Quart. J. Med.*, **19**, 57.

PRIMARY TUBERCULOSIS OF THE GUM

BY

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(Received for Publication May 26, 1950)

Apart from the three cases of primary tuberculous ulceration of the mouth, with involvement of the relevant submaxillary gland, recently reported (January 23, 1950) by Boyes and Miller at a meeting of the Odontological Section of the Royal Society of Medicine but not yet published in the Proceedings of the Society, no record has been found of cases in this country or in the United States of America. A case in this country, therefore, is sufficiently uncommon to merit recording. There was no response to treatment locally but, following the exhibition of streptomycin systemically, the result has been most satisfactory, although it is too early to claim a cure.

In the last 17 years there have been a number of cases published in European countries, amongst which the following may be mentioned: Akerberg (1933), Vallette and Rosenkranz (1936), Quintero (1947), Bernheim and Confavreux (1948), Lebourg and Roy (1949), Raison, Lepoivre, and Chalvet (1949).

Case Report

The case we report is that of a girl, A.J., aged 5 years and 10 months, who was referred to the out-patient department by her doctor because of general malaise for the last few months, associated with gingivitis affecting particularly the lower gums, and a chronic ulcer of the lower sulcus with enlarged submaxillary and cervical glands. The ulcer was known to have been present for eight weeks and was treated locally with penicillin lozenges and generally by a 'tonic' and vitamin C. At the onset some fever was noted. The patient had a habit of sucking the first finger of the right hand which, during the act, rested against the lower right incisor. In view of the contact described below this habit may have been the means of introducing the infection.

Previous History. Delivery had been normal at full term, and the birth weight was 7½ lb. The baby was breast-fed for nine months. The milestones had been normal.

At 1 year she had whooping cough, and at 4 years, measles. She always had a poor appetite and a tendency to dental caries.

In February, 1949, she had two teeth extracted followed by high fever and 'a chill on the bladder'. A tuberculin jelly patch test at this time is reported as having been negative. The test was carried out as the child's doctor wished to exclude abdominal tuberculosis. On recovery the patient remained well until the present episode.

Family History. The mother, father and sister (aged 2 years 11 months) are well. Radiological examination of their chests has revealed no evidence of tuberculosis. The grandmother and great-uncle were tuberculous, but there has been no contact.

Before the oral condition developed the patient had visited a neighbour on a number of occasions. This person is now known to have been suffering from pulmonary tuberculosis, and has since been admitted to hospital for treatment.

The patient had had only pasteurized milk and this had always been brought to the boil before use.

Examination. She was a pale child with evidence of loss of weight (39¾ lb., i.e. 18·1 kg.). Her skin was moist. A painless indolent ulcer, oval in shape, extended from the right lower deciduous canine tooth mesially to the right lower permanent central and from the gingival margin to the base of the sulcus. In the middle of this area there was a flake of hard tissue, probably a piece of necrotic bone in process of separation. This was confirmed later by biopsy. There was gingivitis involving the whole lower gum and enlargement of the submaxillary gland, which was firm, smooth and rounded, an inch (2·5 cm.) in diameter and painless. The nose and throat were healthy, and there was no abnormality in the respiratory, cardiovascular, and central nervous systems, and abdomen.

Because a chronic ulceration of such duration in a child is very unusual the patient was referred to the Eastman Dental Clinic, where a blood count gave haemoglobin 82%, white cells 14,200 per c.mm. (polymorphs 45%, lymphocytes 52%, eosinophils 2%, and monocytes 1%).

Biopsy was performed twice, the first being inconclusive, the second showing 'granulation tissue in which there are several small histological tubercles, with early caseation. Occasional acid-alcohol-fast bacilli were seen in tissues' (Figs. 1-3).

A positive culture was obtained at the end of five weeks. A guinea-pig was inoculated, and in six weeks showed lesions typical of tuberculosis.

In view of the biopsy report, the patient was admitted to the Victoria Hospital for Children, Tite Street, on September 29, 1949. Both the local and general conditions were unchanged from those reported above.

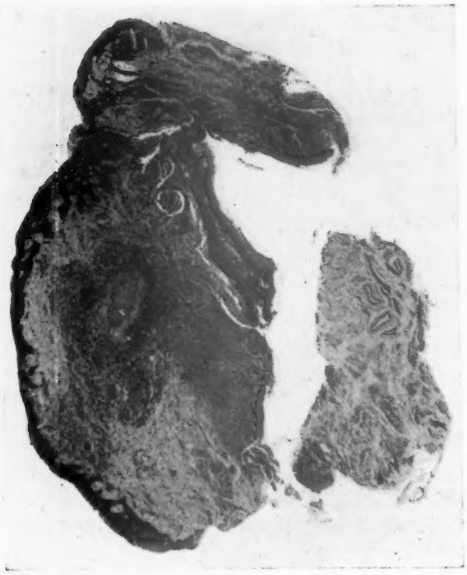

FIG. 1.—Photograph of biopsy specimen showing area of caseation surrounded by giant cell systems.

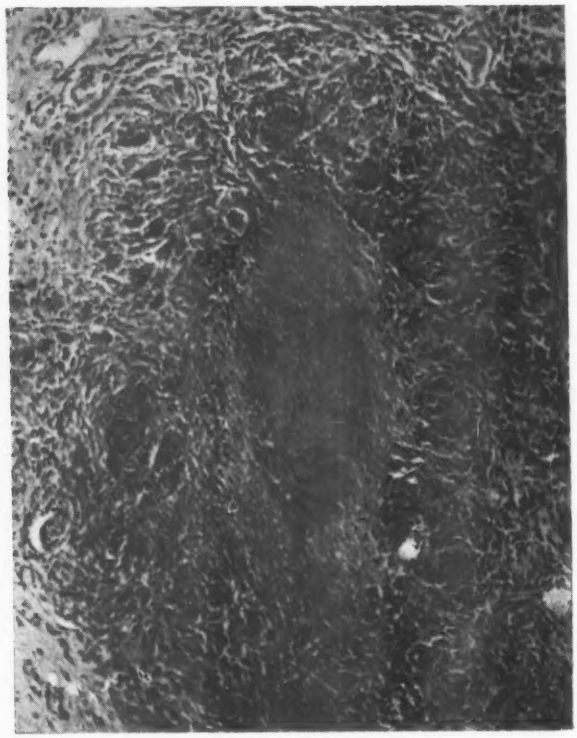

FIG. 2.—High power view showing area of caseation with surrounding giant cell systems.

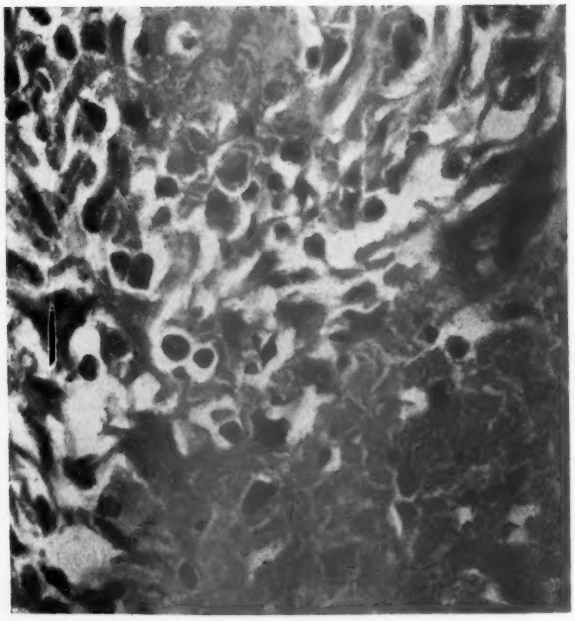

FIG. 3.—High power view to show margin of area of caseation necrosis with adjacent epithelioid cells and giant cells.

The following further investigations were carried out. The Mantoux test, 1:1,000, was strongly positive. No bony abnormality of the jaw was seen radiologically, nor was any abnormality shown in the thorax and abdomen.

A second blood count gave haemoglobin 80%, W.B.C. 14,300 per c.mm. (polymorphs 62%, lymphocytes 33%, monocytes 3%, eosinophils 1%, and Turck, 1%). The E.S.R. was 14 mm. in 1 hour (micro.).

Progress and Treatment. The temperature remained normal during the ten weeks' stay in hospital except for an occasional rise to 99° in the evening. Pulse and respirations were normal throughout.

The patient was kept on bed rest, and the affected area was cleansed with sterile cotton wool. No antiseptics were used.

On October 10, as there was no improvement, streptomycin calcium complex (Glaxo), 0·38 g., b.d.s., intramuscularly, was given for three weeks, the dose being based on the Medical Research Council recommendations of 0·02 g. per lb. body weight per day. The total dose in this course was 17·48 g.

On October 27 the course of streptomycin was completed and the ulcer was almost healed. The gingivitis and general adenitis had subsided. The submaxillary gland had markedly decreased in size and the general health was much improved. The jaw was again examined radiologically and no bony abnormality found.

By November 10 the ulcer was healed, and the gland firm and further reduced in size. Weight gain continued.

There was slight but persistent inflammation round the second lower right deciduous incisor tooth which was found to be loose. It was uncertain whether this looseness was due to natural causes or a sequel to the previous inflammatory condition. It was decided to extract this and two other carious teeth under a streptomycin umbrella. Intramuscular streptomycin, 0·38 g. twice daily, was given for ten days (total 7·6 g.). After the extractions the gums healed satisfactorily and the patient was discharged.

Early in December (December 7, 1949) the child was in good general health (weight 42 lb., i.e. 19·0 kg.); the mouth was healthy and the ulcer remained healed. On the last visit to the out-patient department (January 17, 1950) there had been a further gain in weight of 2 lb. (0·906 kg.), the progress in general health continued, and the mouth was healthy. The right submaxillary gland was now hard, 1 cm. in diameter, and the remaining glands of the neck just palpable with some small shotty glands in both posterior triangles.

Locally the most notable fact was the painless nature of the ulcer and glands. Before streptomycin the ulcer remained in an indolent state, showing no response to local treatment or to vitamins D (approximately 1,200 units daily) and A, and vitamin C by mouth. On investigation, the tuberculous nature of the lesion was proved and no other cause of the patient's general malaise could be found. There was no evidence of a primary tuberculous infection elsewhere.

Discussion

From the literature that has been reviewed, the following observations are interesting.

The cases reported occurred between the ages of 7 and 12 years. They were associated with the loss of the deciduous teeth, or eruption of the permanent teeth in the cases of Åkerberg (1933), Schmiziger (1945), Quintero (1947), Lebourg and Roy (1949), and Raison, Lepoivre, and Chalvet in the same year.

Characteristically there has been found an indolent ulcer of the gum, resistant to local treatment, painless to touch and with enlarged relevant glands with little tenderness on palpation. This latter finding is in contradistinction to the tenderness of glands associated with other infections of the oral cavity (Vallette and Rosenkranz, 1936; Schmiziger, 1945; Quintero, 1947; Bernheim and Confavreux, 1948; Lebourg and Roy, 1949; and Raison, Lepoivre, and Chalvet (1949).

Biopsy of an ulcer was performed by Åkerberg (1933) when typical tubercle formations were demonstrated. These were shown in the case we report, and in addition, acid-alcohol-fast bacilli were found. Tubercle bacilli have been recovered from swabs taken from the ulcers (Bernheim and Confavreux, 1948, and Raison, Lepoivre, and Chalvet, 1949).

Two cases (Quintero, 1947; and Lebourg and Roy, 1949), ended fatally, the first with evidence of both miliary tuberculosis and tuberculous meningitis, and the second with tuberculous meningitis only. In the discussions following the reporting of Lebourg and Roy's case, Bataille (1949) stated that he had found records in the literature of 16 cases of primary tuberculosis of the gum, and in five of these tuberculous meningitis had followed with fatal results. Lebourg and Roy, commenting on this stated that they had had 14 cases in the Trousseau Hospital, Paris, and in only one, that reported above, had meningitis followed.

Åkerberg (1933) pointed out that the glands appear to be enlarged beyond that expected from the indolent nature of the ulcer of the gum. They commented on the tendency of the glandular enlargement in tuberculous infections to be much greated in primary than in secondary infections.

In a number of instances it has been suggested that the infection is acquired from milk. It is often associated with local trauma of the gum due to the loss of the deciduous teeth or eruption of the permanent teeth (Åkerberg, 1933; Schmiziger, 1945; Bernheim and Confavreux, 1948; and Raison, Lepoivre, and Chalvert, 1949). The evidence can only be regarded as circumstantial in the cases quoted. Proof of the recent exposure to infected milk was shown, but in no instance was it established

that the lesion was due to the bovine tubercle bacillus.

In cases where radiological examination of the jaw was carried out no evidence of bony involvement was demonstrated (Vallette and Rosenkranz, 1936; Quintero, 1947; and Raison, Lepoivre, and Chalvet 1949). The case we describe was examined twice, but on each occasion there were no radiological changes to be seen in the underlying bone, although initially the alveolar bone was involved as proved by the biopsy.

In one case (Vallette and Rosenkranz, 1936) within six weeks of the primary infection of the gum being observed the patient developed erythema nodosum.

In the literature reviewed no evidence was advanced of a preceding contact with a case of tuberculosis, although it is not possible to judge from the reports how thoroughly this aspect was investigated in every instance. In the case we describe there was a possible human source of infection.

It is of interest to note that oral tuberculous infection, secondary to a pulmonary lesion, is relatively common and well recognized. Much has been written on this subject, and the paper of Darlington and Salman (1937) provides a comprehensive review of the forms in which it may occur.

Though it is clear that primary tuberculous ulceration of the gum is not a frequent occurrence, the fact that cases have been known to terminate fatally following a generalized spread makes it a condition worthy of note. Since most cases appear to follow a relatively benign course and heal in a way comparable to the majority of primary tuberculous infections elsewhere in the body, it is possible that the condition may occur more often than is recognized, especially in rural areas where milk may not be pasteurized. Perhaps, in some instances, it may be masked by a local secondary infection so that the underlying tuberculous lesion is not recognized.

Summary

A case is described of primary tuberculosis of the gum which responded satisfactorily to streptomycin treatment. The literature is reviewed.

Our thanks are due to Dr. Charles Pinckney for his permission to report this case and for his encouragement and advice in its preparation. We wish to thank Professor R. A. Webb and Drs. M. P. Jevons and I. P. Beswick for the report on the biopsy and subsequent identification of the tubercle bacillus. We also thank Professor John Boyes and Dr. F. J. W. Miller for permission to quote their cases before they appear in the *Proceedings of the Royal Society of Medicine*.

References

Åkerberg, E. (1933). *Acta derm.-venereol., Stockh.*, **14**, 127.

Bataille, R. (1949). *Rev. Stomatol., Paris*, **50**, 368.

Bernheim, M., and Confavreux, J. (1948). *Sem. Hôp. Paris*, **24**, 1206.

Darlington, C. C., and Salman, I. (1937). *Amer. Rev. Tuberc.*, **35**, 147.

Lebourg, L., and Roy, M. (1949). *Rev. Stomatol., Paris*, **50**, 364.

Quintero, J. (1947). *Ibid.*, **48**, 417.

Raison, Lepoivre, and Chalvet (1949). *Ibid.*, **50**, 362.

Schmiziger, P. (1945). French Summary by C. Bonsack. *Schweiz. Mschr. Zahnheilk.*, p. 1,087.

Vallette, A., and Rosenkranz, B. (1936). *Bull. Soc. Pédiat., Paris*, **34**, 465.

THE ELECTRICAL CONDUCTIVITY AND CHLORIDE CONTENT OF WOMEN'S MILK

PART I: METHODS AND PRACTICAL APPLICATION

BY

W. O. KERMACK and R. A. MILLER

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(RECEIVED FOR PUBLICATION JULY 20, 1950)

Few observations have been recorded on the electrical conductivity of women's milk. Koeppe (1898) measured the conductivity of 19 specimens of milk taken from five women who were in various stages of lactation. The values of specimens taken in the first month ranged from 174 to 454×10^{-5} ohm^{-1} cm.$^{-1}$ and those taken during the second to eleventh months varied from 150 to 238×10^{-5} ohm^{-1} cm.$^{-1}$. In the twelfth month only one specimen was taken and that eight days after the infant had ceased to be breast-fed. It had a conductivity of 843×10^{-5} ohm^{-1} cm.$^{-1}$. All these measurements were made at 18°. Jackson and Rothera (1914) made a fuller investigation on the electrical conductivity of milk at 25° taken from 22 women. Their results showed that the conductivity of colostrum was 321 to 391×10^{-5} ohm^{-1} cm.$^{-1}$ and of normal milk was 214 to 315×10^{-5} ohm^{-1} cm.$^{-1}$ and that of one specimen of abnormal milk was 959×10^{-5} ohm^{-1} cm.$^{-1}$. They stated that milk taken in the evening had a lower conductivity than milk taken in the morning, and in five out of six cases the conductivity was higher in the 'after-milk' than in the 'fore-milk' (the after-milk being milk taken after a breast feed and the fore-milk before a breast feed).

It is apparent that conductivity values tend to vary greatly and that the stage of lactation and the time of day or stage of feed at which the specimen is taken may influence the results. It was considered desirable to carry out similar investigations on a much larger series of specimens in order to ascertain more precisely the influence of various factors upon the electrical conductivity. It also seemed of interest to carry out concurrently a series of observations on the chloride content of the milk to determine the relationship between the conductivity of the milk and the chloride value.

Methods

In the series of women investigated, 4-8 ml. of breast milk were expressed just before the infant's first feed in the morning or its mid-day feed, into a container which had been washed, rinsed in distilled water, and dried in an oven. The samples were kept in a cool place and the conductivity of each specimen was measured as soon as possible after it had been obtained. In no case was there a delay of more than 24 hours. Observations showed that no appreciable alteration in conductivity took place during 24 hours, provided the temperature was less than 12° C.

Apparatus for Measuring Electrical Conductivity. To measure the conductivity the milk was placed in a cell and its resistance was measured in the usual way by using a commercial Wheatstone bridge manufactured by Taylor Electrical Instrument Ltd., Slough. The apparatus worked on alternating current at 50 cycles, and the cathode ray indicator or 'magic-eye' incorporated in the apparatus showed when the bridge was balanced. The cell employed was similar to that used by Daly, Eggleton, Elsden, and Hebb (1946). The cells were constructed from glass tubing of $\frac{1}{2}$ in. external diameter and $\frac{3}{8}$ in. internal diameter. The tubing was drawn out and bent to form a U-shaped capillary, parts of the original tubing being left at each end to form two cups. The amount of milk required to fill the cell was about 1 ml.

The two electrodes for the cell consisted of platinum wire. The free ends of the platinum wire were made into loops and immersed in the milk in the cups of the cell, while the other ends were connected to the test terminals on the Wheatstone bridge. Because the resistance in the cell was almost entirely in the capillary portion, the exact position of the electrodes in the two cups did not have an appreciable effect upon the measurements. Furthermore, the resistance was high and the current low, and a quick and accurate measurement of the resistance was easily obtained. The electrodes were kept clean by passing them through an oxidizing flame and by occasionally cleaning them with

concentrated nitric acid. At no time was it necessary to platinize the electrodes.

Calculation of Specific Conductivity of Milk. The milk was placed in the cell, immersed in a water bath, and the resistance measured. A standard temperature of 18° was chosen, as most investigations of this nature in the past have been expressed at that temperature. The change in the resistance of milk per degree change in temperature was found to be 2·1% for whole milk, and 2·0% for partially separated milk, and these corrections were applied when necessary.

The specific conductivity of the milk was calculated from the formula $C=K/R$, where C is the specific conductivity, R the resistance as measured and corrected for temperature, and K the cell-constant. The cell-constant was obtained by measuring the resistance of the cell filled with potassium chloride of known concentration and making use of the specific conductivity value of such salt solution given in the literature. The value of K for the cell employed in our experiments was 249·5.

Effect of Separation of Fat on Conductivity. Jackson and Rothera (1914) have stated that when measuring the electrical conductivity of cow's milk, it is preferable first to remove the fat, because the fat content of milk is variable and the removal of the fat reduces the range of conductivity values. In a series of 20 milk specimens, the fat content ranged from 1·1 to 6·2%. For 1 g. of fat in 100 ml. milk, the electrical conductivity value was reduced on the average 1·93%, and the total reduction in the electrical conductivity of the various milk specimens was 2·12 to 11·97%. When the speed of the centrifuge was approximately 2,500 revolution per minute a rise in conductivity occurred in the first 15 minutes due to the separation of the fat. When these specimens were centrifuged for more than 15 minutes they showed no further change in electrical conductivity. In the present work, therefore, 15 minutes' centrifuging was adopted as a standard period, and a number of observations were made on the effect of the removal of fat in this way. It appeared possible that the range of electrical conductivity values for women's milk might be smaller if fat-free milk were used for the estimations instead of whole milk, and that, consequently, the effect of other factors might be brought out more clearly by the use of fat-free milk.

In a series of specimens, the value of estimating the electrical conductivity of separated milk was assessed. The electrical conductivities of 390 specimens were measured, of which 210 were taken from mothers in the first month of lactation and 180 from mothers in the second to fifth months of lactation. The specimens were both from women with adequate lactation and from those with inadequate lactation. The criterion for adequate lactation on the part of the mother was that her infant gained weight satisfactorily. The infants of mothers with inadequate lactation failed to gain weight, and this failure was shown by test-feeding to be due to the infants receiving less than 2 oz. of milk per lb. of body weight per day. Of the 390 specimens, 233 came from mothers with adequate, and 157 from mothers with inadequate, lactation. After the electrical conductivity of each sample was estimated the sample was centrifuged and its electrical conductivity again determined. The results of the investigations are given in Fig. 1. The values

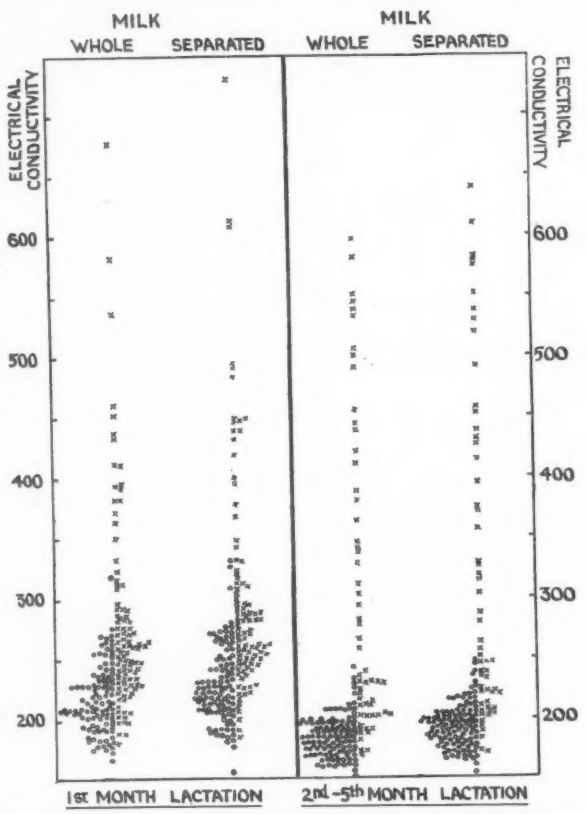

FIG. 1.—Diagram showing that the scatter of results for whole milk is similar to that for separated milk. This applies to values obtained for women with both adequate lactation (O) and to those obtained for women with inadequate lactation (X).

for separated milk are plotted in two groups; those for milk taken from women in the first month of lactation, and those from women in the second to fifth months of lactation. From a comparison of these groups of values for women's milk, it is apparent that the scatter of the results for separated milk does not differ appreciably from that of whole milk, and suggests that there is no conclusive advantage in separating fat from women's milk before measuring conductivity.

Determination of Chloride Content of Milk. The chloride content was estimated by the method described by Patterson (1928). Milk (2 ml.) was mixed with nitric acid (30 ml.) and to this mixture 40 ml. acetone and 10 ml. $^{N}/_{30}$ silver nitrate were added. The excess silver nitrate was titrated with $^{N}/_{60}$ ammonium thiocyanate, three drops of iron alum being added as indicator. The chloride content was calculated in terms of milligrams of sodium chloride per 100 ml. of milk.

Results

The electrical conductivity of the samples of whole milk varied from 150 to 320×10^{-5} ohm^{-1} cm.$^{-1}$ in

mothers with adequate lactation, and from 170 to 675×10^{-5} ohm^{-1} cm.$^{-1}$ in mothers with inadequate lactation. Women with adequate lactation tend to have milk of a lower conductivity than women with inadequate lactation, the mean value of the former being 194×10^{-5} ohm^{-1} cm.$^{-1}$ and of the latter 301×10^{-5} ohm^{-1} cm.$^{-1}$ The chloride content of milk from mothers with an adequate milk supply ranged from 24 to 107 mg. % and had an average chloride content of 57 mg. per 100 ml., whilst the corresponding values for mothers with an inadequate milk supply ranged from 43 to 355 mg. %, and the average chloride content was 135 mg. % (in terms of sodium chloride) per 100 ml. These results on chloride content are in keeping with the observations made by Sisson and Denis (1921), Widdows, Lowenfeld, Bond, Shiskin, and Taylor (1935), and Ishii (1937).

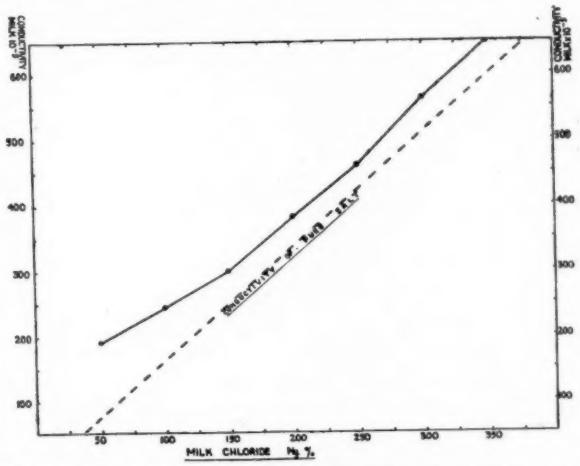

FIG. 3.—Graph showing the relationship of the electrical conductivity of human milk to the electrical conductivity of pure salt solution of the same chloride concentration.

Relation of Electrical Conductivity to Chloride Content. In the present work 668 specimens taken in the first five months of lactation have been examined for both conductivity and chloride content. The results are summarized in Fig. 2 in which the conductivity value for each specimen has been plotted against the chloride value of the same specimen. It is apparent from the figure that the higher the chloride content, the greater, on the average, is the electrical conductivity. This relationship is also exhibited in Fig. 3, which shows the average conductivity value of milk with a given chloride content. Fig. 3 also shows the electrical conductivity of solutions of pure sodium chloride of various concentrations; it will be seen that the conductivity of the milk was greater than that of a solution of pure sodium chloride of the same chloride content. Moreover, the conductivity of milk specimens with a relatively high chloride content tends to approximate more closely to that obtained for a solution of pure sodium chloride of the same chloride concentration than do conductivity values for milks of low chloride content. Thus, when the chloride content is low, the contribution of the other electrolytes to the electrical conductivity of milk becomes more important relatively and absolutely.

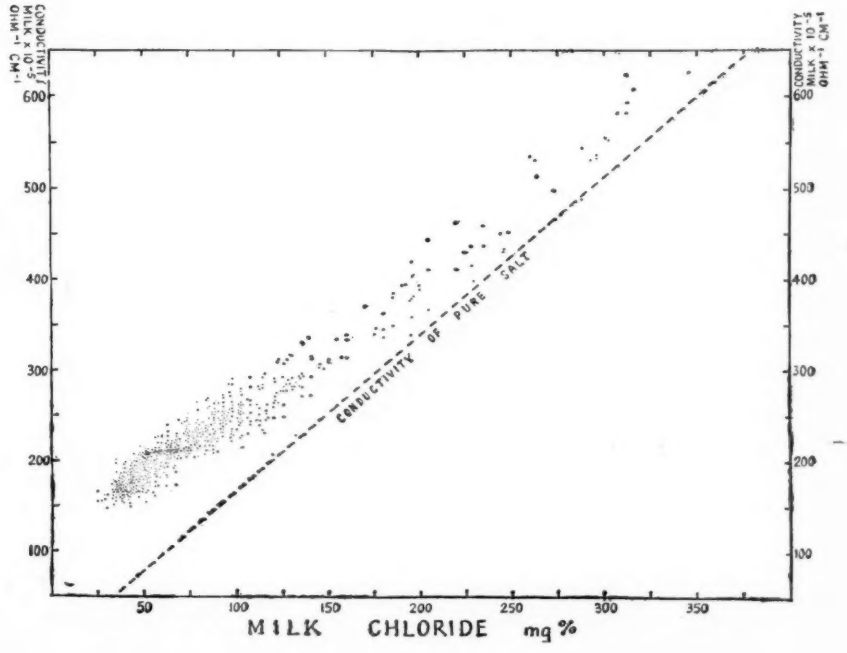

FIG. 2.—Graph showing the relationship between the electrical conductivity of human milk and its chloride content.

Discussion

The conductivity of an aqueous solution depends on the number and nature of the ions present and also on the viscosity of the aqueous medium through which they move under the influence of the electric field. The chloride ion is the one which is most plentiful in milk and is said to account for either 57% (Flohil, 1911), or 49 to 78% (Coste and Shelbourn, 1919) of the conductivity of cow's milk. In milks which have been secreted by diseased glands, it is the chloride content which is usually increased at the expense of constituents such as lactose, and so in these milks the conductivity is raised. It is, therefore, not surprising that high conductivity is characteristic of milk produced by mothers whose lactation is inadequate.

Although non-electrolytes, such as sugar and fats, do not directly contribute to the electrical conductivity, they affect it through their influence on the viscosity. In general, the effect of the presence of compounds with relatively large molecules, such as proteins or lactose, is to raise the viscosity compared with that of pure water. The effect, however, of variations in the protein and lactose content of milk on the electrical conductivity is relatively small compared with that of variation in salt content. In both women's milk and cow's milk it has been found that the conductivity falls as the lactose content increases (Schweers, 1932, and Jackson and Rothera, 1914). Schnorf (1904) states that the protein present in cow's milk reduces its conductivity by 10 to 17%, while Bagarsky and Tangl (1898) and Jackson and Rothera (1914) found a fall of 2·5 to 2·75% in the conductivity for every gram of protein present. Our results suggest that, on the average, every 1% of fat reduces the conductivity by about 2% for human milk, whilst Taylor (1914) found a corresponding reduction of 2·3% for cow's milk.

A more important influence on the conductivity of an aqueous solution is that produced by variations of temperature, mainly as the result of the change of viscosity when the temperature is varied. The change in electrical conductivity of milk was found to be approximately 2% per degree.

A high chloride content or conductivity is a strong indication of inadequate lactation, but there is a considerable overlap between the values for mothers with adequate and those with inadequate lactation. Electrical conductivity can be measured quickly and accurately and is particularly suitable for clinical use, as the apparatus involved is compact, relatively inexpensive, and simple to operate, and it would appear that the measurement is a useful adjunct in investigating problems of lactation.

Summary

The electrical conductivity of over 700 samples of women's milk has been measured by the convenient method used by Daly *et al.* (1946), and their chloride content has also been determined. The electrical conductivity values are given for a temperature of 18°, a correction being applied to the observed values when readings were made at temperatures different from 18°.

The removal of the milk fat by centrifugation results in an increase in conductivity, the average increase being 1·93% per gram of fat. Though the removal of fat eliminates a variable factor affecting the electrical conductivity, the gain in uniformity of results is not appreciable.

The electrical conductivity of women's milk shows considerable variation, the range observed extending from 150 to 675×10^{-5} ohm^{-1} cm.$^{-1}$ The lower values generally found for mothers with adequate lactation and the higher values are more characteristic of mothers with inadequate lactation. There is, however, a certain overlap between the two groups.

The chief factor influencing the electrical conductivity of women's milk is the chloride content. The conductivity of milk does not bear a constant relationship to salt solution of the same concentration, the relationship being closer when the chloride of milk is high than when it is low. The effect of other factors is discussed.

The electrical conductivity of women's milk affords information as to its quality comparable with that given by estimation of its chloride content. In view of the ease and rapidity with which the conductivity can be measured its determination is recommended as a valuable aid in assessing the quality of the milk.

We should like to thank Professor R. W. B. Ellis for his criticism and advice, the nursing staff of the Simpson Maternity Memorial Pavilion, the Royal Infirmary, Edinburgh, for collecting many of the milk samples, and the Laboratory of the Royal College of Physicians, Edinburgh, for the facilities granted to us to carry out the work dealt with in this series of papers. We also wish to thank Dr. A. Comrie, College of Agriculture, Edinburgh, for estimating the fat content of milk samples.

An account of the investigations in this and subsequent parts was embodied in a thesis for the degree of Ph.D. (1949) by R. A. Miller, Edinburgh.

References

Bagarsky, and Tangl (1898). Cited by Jackson and Rothera, 1914.

Coste, J. H., and Shelbourn, E. T. (1919). *Analyst*, **44**, 158.

Daly, I. de B., Eggleton, P., Elsden, S. R., and Hebb, C. O. (1946). *Quart. J. exp. Physiol.*, **33**, 215.

Davies, W. L. (1936). 'The Chemistry of Milk,' pp. 269-270. London.

Flohil, J. T. (1911). *Chem. Weekbl.*, **8,** 605; and *Chem. Abstr.*, **5,** 3598.
Ishii, M. (1937). *Tohoku J. exp. Med.*, **31,** 580.
Jackson, L. C., and Rothera, A. C. H. (1914). *Biochem. J.*, **8,** 1.
Koeppe, H. (1898). *Jb. Kinderheilk.*, **47,** 389.
Patterson, J. (1928). *Biochem. J.*, **22,** 758.
Schnorf, C. (1904). 'Physikalisch-chemische Untersuchung physiologischer und pathologischer Kuh-Milch.' Dissertation. Zurich. Cited by Jackson and Rothera, 1914.
Schweers, A. (1932). *Arch. Hyg. Berl.*, **107,** 354.
Sisson, W. R., and Denis, W. (1921). *Amer. J. Dis. Child.*, **21,** 389.
Taylor, H. B. (1914). *J. Roy. Soc. N.S.W.*, **47,** 174. Cited by Davis, 1936.
Widdows, S. T., Lowenfeld, M. E., Bond, M., Shiskin, C., and Taylor, E. I. (1935). *Biochem. J.*, **29,** 1145.

BRITISH PAEDIATRIC ASSOCIATION

PROCEEDINGS OF THE TWENTY-SECOND GENERAL MEETING

The twenty-second annual meeting of the British Paediatric Association was held at Windermere on April 18, 19, and 20, 1951.

Business Proceedings. The President, Professor Sir James Spence, was in the chair and the following members were present:

Drs. F. M. B. Allen, E. C. Allibone, I. M. Anderson, H. T. Ashby, C. Asher, H. S. Baar, T. E. D. Beavan, J. M. Bligh, M. Bodian, R. E. Bonham Carter, F. Braid, J. V. Braithwaite, R. W. Brookfield, D. Browne, W. H. P. Cant, N. B. Capon, I. A. B. Cathie, C. Chisholm, T. Colver, B. D. Corner, J. Craig, W. S. Craig, M. Creak, J. Crooks, V. M. Crosse, G. Davison, A. C. Doyne Bell, R. W. B. Ellis, J. L. Emery, P. R. Evans, T. Y. Finlay, G. B. Fleming, F. J. Ford, A. W. Franklin, D. Gairdner, W. F. Gaisford, E. Gorter, S. Graham, C. K. J. Hamilton, C. F. Harris, E. W. Hart, J. D. Hay, J. L. Henderson, D. V. Hubble, J. H. Hutchison, R. S. Illingworth, N. M. Jacoby, H. Everley Jones, F. F. Kane, R. Lightwood, P. MacArthur, A. MacGregor, H. M. M. Mackay, R. Mac Keith, R. A. McCance, R. Marshall, F. J. W. Miller, R. A. Miller, A. Moncrieff, A. V. Neale, G. H. Newns, A. P. Norman, A. G. Ogilvie, J. N. O'Reilly, C. G. Parsons, W. W. Payne, C. B. Perry, C. P. Pinckney, C. T. Potter, B. Schlesinger, W. Sheldon, U. Shelley, V. Smallpeice, W. C. Smallwood, J. M. Smellie, R. E. Smith, J. C. Spence, R. E. Steen, H. H. Stewart, K. H. Tallerman, M. L. Thomson, C. W. Vining, H. K. Waller, A. G. Watkins, H. Parry Williams, T. P. Williams, D. W. Winnicott, W. F. Young.

The Association had the honour of entertaining 24 paediatricians from Holland as well as 30 other guests from the British Isles.

The minutes of the last Annual General Meeting were approved.

ELECTION OF OFFICERS. The following were elected by ballot for the year 1951-52.

PRESIDENT. Professor N. B. Capon.

TREASURER. Dr. R. C. Lightwood.

SECRETARY. Professor Alan Moncrieff.

EXECUTIVE COMMITTEE (new members).

REPRESENTATIVE FOR LONDON. Dr. R. H. Dobbs.

REPRESENTATIVES FOR THE PROVINCES. Professor A. V. Neale (Bristol); Dr. R. E. Smith (Rugby).

REPRESENTATIVE FOR SCOTLAND. Professor J. L. Henderson (St. Andrews).

ELECTION OF NEW MEMBERS. The following were elected by ballot to membership of the Association:

(a) HONORARY MEMBERS

Dr. H. S. Banks
Dr. C. K. J. Hamilton
Sir James Spence
Dr. W. G. Wyllie

(b) CORRESPONDING MEMBERS

Dr. James Gamble (Boston)
Prof. A. Goldbloom (Montreal)

(c) ORDINARY MEMBERS

Dr. W. A. B. Campbell (Belfast)
Dr. S. Doxiadis (Sheffield)
Dr. R. Gordon (Sheffield)
Dr. J. Hart-Mercer (Newcastle-upon-Tyne)
Dr. R. A. Shanks (Glasgow)
Dr. R. M. Todd (Liverpool)
Mr. R. B. Zachary (Sheffield)

The TREASURER'S REPORT was received and approved.

The REPORT OF THE EXECUTIVE COMMITTEE was received and approved and is printed below.

NEXT MEETING. Suggestions were made to hold the 1952 meeting at Porthcawl or at Newcastle, County Down. It was agreed to leave this to the Executive Committee.

DISCUSSION ON POLICY. It was suggested that time should be provided for discussions on matters of policy.

Report of the Executive Committee 1950-51

1. During the year the Association has sustained a heavy loss by the deaths of the following: Charles Box (honorary member), Herbert Morley Fletcher (original member and past-president), Leonard Gregory Parsons (original member and past-president), John Forbes Ward (original member), Kenneth Douglas Wilkinson (original member), A. Eckstein (Hamburg—corresponding member), L. Exchaquet (Lausanne—corresponding member) and A. Lichtenstein (Stockholm—corresponding member).

2. The Association will wish to congratulate the President, Sir James Spence, on his well merited distinction; Dr. Harold Waller on being awarded the Dawson Williams Prize of the B.M.A.; and Dr. J. L. Henderson on his election to the James

Mackenzie Chair of Child Health at the University of St. Andrews.

3. The Executive Committee has met on three occasions since the last Annual General Meeting held in Windermere in April, 1950, and some account of the business transacted is summarized in this report.

4. NURSING OF SICK CHILDREN. Representations to the General Nursing Council and to the Ministry of Health regarding the appointment of a paediatrician or a sick children's nurse to each area nurse-training committee have not been entirely successful, and members are urged to make sure that no attempt is made in any area to reduce the opportunities for the training of sick children's nurses.

5. ARCHIVES OF DISEASE IN CHILDHOOD. It was recommended to the Editorial Committee of the *Archives* that from January, 1951, Dr. W. W. Payne and Prof. A. G. Watkins should replace Dr. Helen Mackay and Prof. Sir James Spence. Dr. P. R. Evans, as senior editor, was co-opted to serve on the Executive Committee for a period of two years.

6. INTERNATIONAL PAEDIATRIC CONGRESS. British paediatricians and others numbering between 40 and 50, many of them members of the Association, attended the Sixth International Paediatric Congress in Zurich in July, 1950. Altogether there were nearly 2,000 representatives from 56 different countries. Communications from British representatives appeared to be well received. A provisional constitution for the formation of an International Paediatric Association was approved for ratification at the next International Congress which is to be held in Havana in 1953. Each national association is asked to subscribe one Swiss franc for each member annually for the expenses of the International Association. The World Health Organization has officially recognized the I.P.A.

7. TRAINING OF PAEDIATRIC CONSULTANTS. A final report has been approved and will be printed in the *Archives*. Copies have been sent to the Royal College of Physicians, the General Medical Council, the Ministry of Health, and the Department of Health for Scotland.

8. PREMATURITY. The Joint Standing Committee on Prematurity of the R.C.O.G. and this Association has produced a memorandum on the care of premature babies in urban and rural areas which it is hoped to publish. Advice has also been given to the Ministry of Health on the preparation of a form for national use for a return of hospital statistics on premature infants. It has also instigated an investigation into retro-lental fibroplasia.

9. MENTAL DEFECT IN CHILDREN UNDER TWO YEARS. The members of the Child Psychology Sub-Committee prepared a report on this subject, which was approved by the Executive Committee and submitted to the National Association for Mental Health. It is proposed to produce a pamphlet on this subject suitable for paediatricians.

10. HEIGHT AND WEIGHT SURVEY. As has been announced in the press, an investigation of heights and weights of children, sponsored by a joint committee of this Association with the Ministries of Health and Education, is now in progress.

11. OTHER ACTIVITIES. The Association was consulted by the Ministry of Health about the dosage of Vitamin D and a sub-committee reported to the Executive Committee that no change should be made. The Ministry of Education has asked for detailed replies to certain questions for its special committee on maladjusted children and a sub-committee has been appointed to prepare suitable evidence. The joint committee on convalescent homes (with the Invalid Children's Aid Association and the Institute of Almoners) decided to inform the Metropolitan Regional Hospital Boards that children under the age of two should only be sent to convalescent homes if adequate nursing and medical care were available. The sub-committee on tuberculosis is in touch with the Central Council for Health Education regarding the preparation of a pamphlet on prevention. The British Standards Institution continues to consult the Association on instruments and apparatus and suitable members continue to give valuable advice.

12. In accordance with the rules certain changes in the composition and officers of official standing sub-committees have been made by the Executive Committee and details of these changes will be incorporated in the next edition of the Association's booklet.

Scientific Communications

PROF. E. GORTER (Leiden). 'Familial Galactosuria.' This interesting syndrome is characterized by an anomaly of galactose metabolism and signs of hepatic dysfunction.

Soon after birth a tendency to bleeding, failure to gain weight, frequent bouts of vomiting and diarrhoea, enlargement of liver and spleen, galactosuria, hyperbilirubinaemia, albuminuria, and bilateral cataract develop.

We have observed three children in one family. The first died at 7 days, with haemorrhages. The second died at 5 weeks from liver cirrhosis and steatosis with thrombopenia and haemorrhages. The third child was born with haemolytic disease of the newborn, and showed no symptoms after exchange transfusion. The fourth also had haemolytic disease. In both cases it was due to an

A-O antagonism. From the eleventh day of life mellituria and liver dysfunction, gradually increasing in severity, were observed. The child died. The sugar in his urine was proved to be galactose.

It is difficult to decide whether the A-O antagonism or the galactosaemia was responsible for the steatosis and cirrhosis of the liver found at necropsy.

Recently we saw another case of galactosuria. A premature baby developed on the seventh day severe haematemesis with thrombopenia (47,000 and 55,000 per c.mm.), prolonged coagulation time and bleeding time, and normal prothrombin time. There was no blood group antagonism. These symptoms were followed by jaundice, enlargement of the liver and spleen, and by galactosuria.

After withdrawal of all lactose from the diet on the tenth day the general condition improved and the galactosuria disappeared, but the child died four days later. At necropsy the typical symptoms of the disease were found.

The most interesting family was observed by P. K. de Haas, of Goes (Walcheren). All the 10 children with the exception of the second died some days or weeks after birth. In four children galactosuria was observed. The tenth child, born in 1950 (birth weight 2·5 kg.), had from the fourth day presented jaundice and galactosuria with a large liver and bloody stools. He also had cataract. He died, 7 days old, although lactose was omitted from the diet, and at necropsy the liver showed steatosis and some cirrhosis.

Galactosaemia must be considered as an inborn error of metabolism of galactose. Symptoms are due to the toxic effect of the galactose that damages liver and kidney, and not to primary hepatic dysfunction.

DR. JOHN GERRARD (Birmingham). 'The Blood Sugar Level in Haemolytic Disease of the Newborn.' Many suggestions have been put forward to try to explain the development of kernicterus associated with haemolytic disease of the newborn; because none are entirely satisfactory it was decided to study the level of the blood sugar in haemolytic disease, for the brain is dependent on glucose for its metabolic substrate and it was hoped that a study of the blood sugar might provide a clue to the aetiology of kernicterus. The first case to develop hypoglycaemia also developed kernicterus. Treatment was therefore instituted to maintain the blood sugar at normal levels in succeeding cases; this, however, did not prevent the development of kernicterus. In 23 cases studied there was no dramatic fall in the blood sugar level, and yet one of these developed kernicterus; in a further 10 cases the blood sugar fell to an appreciable extent, and though four of these developed kernicterus, it cannot be due to hypoglycaemia *per se* for it may occur even when the blood sugar does not fall to low levels.

As there is a remarkable similarity between the babies of diabetic mothers and those with haemolytic disease, it is suggested that in those with haemolytic disease, as in babies of diabetic mothers, placental function is impaired, the serum oestrogens fall, and the maternal anterior pituitary over-acts thus suppressing hexokinase activity in the infant and leading to the islet hyperplasia found in haemolytic disease. The excess anterior pituitary hormone in the foetal circulation may interfere with the cerebral uptake of glucose and kernicterus may result from an interplay of the blood sugar level and the levels of circulating insulin and diabetogenic or growth hormone.

DR. J. H. P. JONXIS (Rotterdam). 'The Influence of Differences in Food on the Amino-acid Excretion of the Infant.' A child who is getting breast milk excretes only small amounts of free amino-acids in its urine (4 mg. α-amino-nitrogen/100 ml.) except during the first days of life when the excretion is considerably greater. This greater excretion of amino-acids during these first days may be the result of lack of food. Beside free amino-acids some amino-acids in the form of conjugates or peptides are present. When cow's milk is given the excretion of amino-acids is greater, even when the total amount of protein which the child gets is the same as that which it gets from breast milk. This higher excretion is mostly the result of a greater excretion of peptides. When cow's milk is given without vitamin C the total excretion of amino-acids rises still higher.

Of the urines of these two groups of infants two dimensional paper chromatograms were made. It was found that in children who were getting human milk, glycine, serine, alanine, histidine and proline were excreted as free amino-acids in somewhat greater quantity. In nearly all these cases taurine could be demonstrated. When cow's milk was given, taurine could not be demonstrated, but in addition to the amino-acids above mentioned there was a marked excretion of lysine.

DR. R. E. BONHAM CARTER and MR. D. WATERSTON (London). 'The Treatment of Patent Ductus Arteriosus in Infants under the Age of Five Years.' In 761 patients with congenital heart disease a clinical diagnosis of P.D.A. was reached in 85, or 11%. In 46 patients P.D.A. entered the differential diagnosis. Of the 85 patients with P.D.A. 71 had typical continuous murmurs: 12 of these developed under observation; 10 of these had distinct mitral diastolic murmurs at the apex. Three patients have shown marked right axis deviation electrocardiographically.

The indications for operation have been a radiological increase in heart size, a history of diminishing exercise tolerance and, in the babies, a failure to thrive.

It has been our experience that the operation for ligation of the patent ductus arteriosus is easier to carry out, and is better tolerated, under the age of 5 years.

The reasons for this are (1) the ductus is more easily exposed and dissected, (2) it is safer because the tissues are more elastic and not so readily torn, (3) the post-operative complications are fewer, (4) treatment is completed before school age.

Fifty-one cases have been operated on; in all cases the ductus was ligated; 14 of these children were under the age of 5 years.

There have been no deaths and no cases of recanalization.

Post-operative complications have been few and there have been none in those under 5 years.

All cases operated on have been improved clinically with decrease in heart size.

DR. A. HOLZEL (Manchester). 'Follow-up of 200 cases of Pink Disease.' Of 200 patients, 37 had died and of the remaining 163, 110 were re-examined. Eighty were found to have developed normally physically and mentally. Thirty showed various psychosomatic disorders.

Fifteen per cent. of the cases had some relationship with the allergic diathesis. No second attack was recorded. Of 97 cases, 50% had a history of mercury exposure, and 62·5% excreted mercury in abnormal quantities in their urine, whilst only 7% of healthy infants in Manchester and Salford, and 37% in Warwickshire, ingested mercury in teething powders. It was evident that mercury was a relevant factor in the aetiology of acrodynia but not necessarily a causal one. In some cases prolonged mercury ingestion may produce signs and symptoms similar to pink disease. The raised serum cholesterol level, when present, may serve as an indication for B.A.L. treatment.

DR. F. J. FORD (Glasgow). 'Red Finger Tips in the Neonatal Period.' Redness of the terminal phalanges of the fingers during the neonatal period was described and its significance discussed. It is not seen in normal babies after the second or third day of life.

The redness was shown to be associated with a variety of other upsets—vomiting, diarrhoea, fever, loss of weight, upper respiratory catarrh, and paronychiae. Charts were shown demonstrating the association of these abnormalities with the time of appearance of the finger redness. It was suggested that the redness should be regarded as an early indication of infection, probably respiratory infection, and as an indication for the institution of anti-infective treatment. Big babies might not require any treatment but small or feeble infants should be treated as soon as redness of the fingers is noted.

The conclusion was drawn that examination of the finger tips during the neonatal period is an important and helpful procedure.

DR. T. E. OPPÉ (London). 'The Effect of Hypoxia and Hyperoxia on the Respiration of the Newborn.' Dr. Cross and I have studied the effect of differing oxygen concentrations on the minute volume, respiration rate, and tidal air, of full term and premature infants, using the body plethysmograph of Cross (1949) and applying the required gas mixture (100% O_2, 15% O_2 with 85% N_2) by the technique of Cross and Warner (1951).

With the sudden application of 100% oxygen, both the premature and the full term infant show immediate diminution in pulmonary ventilation, which is slightly, though not significantly, greater in small prematures (<4 lb.). In all groups there is a subsequent stimulation of respiration with a significant rise in minute volume.

During the inhalation of 15% oxygen in the inspired air, all groups show an immediate rise in minute volume, which is not well maintained in any group, but least in the premature.

When premature infants are given 100% oxygen immediately after five minutes on 15% oxygen, there is a marked reduction in the minute volume which is significantly more marked in the infants of less than 4 lb. than in those between 4 lb. and 5½ lb.

It is tentatively suggested that there is an active carotid body reflex in the full term and premature infant, but that this reflex accommodates more completely in the premature than in the full term infant.

REFERENCES

Cross, K. W. (1949). *J. Physiol.*, **109**, 459.
——, and Warner, P. (1951). In the press.

DR. K. W. CROSS (London). 'Treatment of Asphyxia Neonatorum by Electrical Stimulation of the Phrenic Nerve.' An instrument was described which is capable of electrical stimulation of the phrenic nerve, and the technique of its application in performing artificial respiration in the newborn was noted.

The results of 30 experiments in the treatment of asphyxia neonatorum, together with the appropriate case histories and subsequent course of these infants, were given.

The infants were simply classified as slightly, moderately and severely ill, and of 30 infants, 26 recovered. In 19 of these, measurements of the

current required to achieve diaphragmatic movement were taken. It was found that, in general, a stronger stimulus was required in order to evoke a response in the severely ill babies than in the slightly ill. There were nine infants in the severely ill group, of whom four died; all the infants in the other groups survived. All the infants who died showed evidence of some pulmonary inflation and had pathological lesions other than asphyxia.

Electro-phrenic stimulation with this apparatus appeared to be successful in achieving pulmonary inflation, without risk of pulmonary emphysema or distension of the stomach, by calling into play the normal muscles. There has been no evidence of any ill-effects at the time of stimulation or subsequently.

DR. D. GAIRDNER (Cambridge). 'Erythropoiesis in Infancy.' Twenty-five healthy infants were followed from birth to 3 months, and from these 102 samples of tibial marrow and the same number of venous blood samples were examined. The marrow erythroid count (the number of nucleated red cell precursors per c.mm. of marrow aspirate) was used as an index of erythropoietic activity. It was shown that the changes in Hb. and red cells from birth to 3 months could be accounted for solely on the basis of changes in the level of erythropoiesis.

Evidence from various sources suggested that erythropoiesis is governed by the oxyhaemoglobin level of arterial blood. In late foetal life arterial blood is probably about 65% oxygen saturated, so that the oxyhaemoglobin level is about 11·5 g. %. From 2 to 18 months the haemoglobin is maintained at a roughly constant level of about 12 g. %, or, since, arterial blood is 95% oxygen saturated, at a level of about 11·5 g. % of oxyhaemoglobin.

Thus in both the foetus and the infant up to 18 months, erythropoietic tissue can be regarded as 'set' to maintain an oxyhaemoglobin level of about 11·5 g. %, and on this assumption the changes in the blood picture after birth are found to be those which would be anticipated.

PROF. A. TEN BOKKEL HUININK (paper read by Dr. W. K. Dicke, of Utrecht). 'Excretion of Fat in Coeliac Disease.' Observations on the effects of wheat flour and wheat starch on fat-absorption, and on the differences between the absorption of saturated and unsaturated fatty acids, are to be reported elsewhere.

DR. A. RUSSELL (London). 'A Diencephalic Syndrome of Emaciation in Infancy and Childhood.' The cardinal feature of a syndrome presenting in infancy in a series of five children was profound emaciation linked in all with initial growth acceleration, and in four with locomotor overactivity and euphoria. There is uniformity also in lesser features including skin pallor associated with a normal haemoglobin (akin to adult hypopituitarism), hypotension, and hypoglycaemia.

All appear to share a common pathological basis in the shape of a neoplastic process directly and predominantly involving the anterior hypothalamus, and indirectly the hypophysis. In four, craniotomy has confirmed the gross location, biopsy revealing astrocytoma in each. Precise delineation of their limits within the diencephalon must await necropsy. In the fifth case ventriculography has exposed the gross anterior filling defect of the third ventricle characterizing previous cases, and craniotomy is planned.

One mechanism underlying the emaciation is a disproportionately enhanced energy output, the result of locomotor overactivity and increased basal metabolism confirmed in repeated studies. That a contributory role is played by anterior pituitary defect, especially of its anabolic function in tissue protein synthesis, was suggested by results of treatment with an anabolic steroid, and by the detection of pituitary functional impairment.

Experimental studies have reproduced most of the ingredients of this symptom complex by lesions in anterior hypothalamic areas, all readily encompassed by a small organic lesion. Furthermore, euphoria and the absence of natural shyness and hostility may be induced by organic interruption of the fronto-thalamo-hypothalamic circuit simulating leucotomy, or lesions confined to the dorsomedial thalamic nuclei (Spiegel, Wycis, Marks, and Lee, 1947).

Diagnosis is not invalidated by the absence of conventional signs of intracranial hypertension. The recognition of this symptom-pattern may afford an opportunity of diagnosis even years before these signs appear. Fuller study of a possible diencephalic mechanism, other than neoplastic, underlying other examples of emaciation may be encouraged by the correlation illustrated.

REFERENCE

Spiegel, E. A., Wycis, H. T., Marks, M., and Lee, A. J. (1947). *Science*, **106**, 349.

DR. J. SLOOFF (Eindhoven). 'Healing of Bronchiectasis.' Thirty-two bronchiectatic children aged under 10 years were re-examined by bronchography from two to 16 years later. In chronic cylindrical bronchiectasis spontaneous recovery is uncommon, but improvement is possible even if there is moderate sacculation. Often the dilatation becomes stationary and produces no symptoms. To cure the bronchial infection and to prevent relapse, the upper air passages should be treated;

postural drainage should be used, and appropriate antibiotics should be instilled into the trachea over a long period. This treatment produced improvement in saccular bronchiectasis. In 10 cases of cylindrical bronchiectasis three patients were cured, and five showed improvement. The two who did not respond had bronchial stenosis.

MR. DENIS BROWNE (London). 'Lymphangioma.' Congenital abnormalities of the lymphatic system may be classified into four types: (1) the cystic lymphangioma or cystic hygroma; (2) the cellular lymphangioma, which may consist of either a solid mass or a diffuse thickening; (3) mixed types of cellular and cystic lymphangioma; (4) congenital lymphatic obstruction, which usually is found in the lower limbs, and causes swelling of the feet which is obvious at birth.

Lymphangiomata vary rapidly in size, due to infection and sudden bleeding into a cyst. When they are in the neck this may be dangerous to life as they obstruct the air passages. In the speaker's experience they have no tendency to spontaneous disappearance following infection, as is so often stated.

Treatment of the cysts is either by aspiration and injection of a sclerosing solution, such as quinine urethane, or by excision.

Treatment of the cellular and mixed types is by excision. X-rays have no effect upon them.

Slides of various types were shown and their histories discussed.

DR. G. M. H. VEENEKLAAS (Utrecht). 'Cause and Sequelae of Intrapulmonary Shadows in Primary Tuberculosis.' It is known that lobar and segmental pulmonary shadows in primary tuberculosis are the result of a tuberculous lesion of the bronchus. We think that the same applies to all shadows in primary tuberculosis with the exception of the Ghon focus, haematogenous spreads, and some perihilar shadows developing as the direct result of a tuberculous lymph node on the surrounding lung tissue. It is evident that bronchial tuberculosis is more frequent even than pulmonary shadows in primary tuberculosis.

The majority of cases of primary tuberculosis heal completely both clinically and radiologically. Does bronchial tuberculosis usually heal without sequelae as well? Of a total of 50 patients, now in good health who had their shadow one to 16 years ago, 30 showed residual bronchial lesions—stenosis, ectasia, distortion, considerable lobar shrinking, hypertrophy of bronchi. Attention is drawn to the high frequency of stenosis, lobar shrinking, and bronchial hypertrophy which have seldom been seen hitherto. Being partly dependent on gravitation, drainage is best in the upper lobes, less in the middle, and least in the lower lobes. Symptoms are seen to decrease in inverse order.

It is concluded that complete recovery from primary tuberculosis may conceal severe residual bronchial lesions which are liable to cause complaints in middle or old age.

DR. G. A. NELIGAN (Newcastle-upon-Tyne). 'Non-tuberculous Osteitis of the Spine.' This paper describes the clinical features of an inflammatory lesion of the lumbar spine studied in six children between the ages of 1 and 2½ years. The disease has a gradual onset and bears a striking resemblance to Pott's disease, from which it may be distinguished by a negative tuberculin skin test, and a much shorter and more benign course. A notable feature of the symptomatology is the frequent occurrence of a hip syndrome grafted on to the basic pattern of the spine syndrome, but without any hip lesion. Evidence is put forward, chiefly from the literature, that *Staphylococcus aureus* is the probable causal agent; but penicillin does not appear to have any striking effect on the course of the disease. Reasons are given for treating the cases by immobilization in plaster during the active stage of the disease; but it should be possible to allow resumption of normal activity within about three months of the onset in most cases. The prognosis for function seems to be excellent, but radiographs are likely to show permanent changes.

PROF. R. S. PILCHER (London). 'Treatment of Hiatus Hernia.' A syndrome, dating from birth, of vomiting during and after meals, with varying amounts of bleeding and sometimes progressing to stricture formation, has been found to be associated with a sliding hiatus hernia and displacement of the cardia into the chest. That the oesophagus is not short but retracted is suggested by the laxity of the vagi. The vomiting may be projectile and simulate pyloric stenosis. Haemorrhage may be severe enough to endanger life. Reflux of the gastric content through an incompetent cardia is thought to be the cause of the symptoms. Reflux can be demonstrated radiologically, and the high position of the cardia and the degree of oesophagitis by oesophagoscopy.

An attempt has been made to treat the syndrome by repair of the hernia and replacement of the stomach below the diaphragm. The immediate results are good, but the operation alone cannot be expected to cure a stricture, although it may make its treatment by dilatation more rewarding. Of 11 cases treated, five had been previously diagnosed as pyloric stenosis. In five, operations had been done on a wrong diagnosis. A plea is made for more precise diagnosis of neonatal vomiting and for correction of the hernia before stricture develops.

BRITISH PAEDIATRIC ASSOCIATION

MEMORANDUM ON THE CARE OF PREMATURE BABIES IN URBAN AND RURAL AREAS

This memorandum has been prepared by the Joint Standing Committee on Prematurity of the Royal College of Obstetricians and Gynaecologists and the British Paediatric Association.*

A complete programme should include a preventive section as well as a care section. This memorandum only deals with the latter. Before good care for the premature baby can be expected the standard of care for mature infants must be raised, but this important aspect is not dealt with here.

A complete care programme for each region or agreed area should include the following: (1) assessment of requirements; (2) hospital care; (3) home care; (4) transport; (5) follow-up care; (6) integration with other health services; (7) education of (*a*) professional personnel and (*b*) parents; (8) research; (9) regular appraisal of results.

The initial steps in the development of a premature baby care programme should be related to the pattern of maternity care in the area concerned, depending on whether the larger proportion of births is in hospitals or at home, and the initial programme, whether it be one of hospital or home care, should be expanded as facilities become available.

Assessment of Requirements

The needs of any area can be estimated if the following data are available: (1) live birth rate; (2) incidence of liveborn premature infants; (3) weight distribution of premature infants; (4) percentage of premature babies born (*a*) in hospital and (*b*) at home; (5) length of care required for premature babies (*a*) in hospital and (*b*) at home.

In case these data are not available for any particular area the following general statements may be used.

Incidence of Prematurity. The incidence of liveborn prematures is usually 5%-7% of the total births, being higher in urban than in rural areas.

Weight Distribution. Twenty to twenty-five per cent. of all premature infants weigh less than 4 lb. at birth and should have the benefit of hospital care if this be possible. (Babies under this birth weight have no cough reflex and may die from regurgitation and inhalation if not kept under constant expert supervision.)

Length of Care Required. The average duration of stay in a hospital unit which deals with a high proportion of the smaller babies is five weeks, and one hospital cot should be provided for every ten babies to be treated annually.

The average duration of domiciliary care required for infants weighing 4 lb. or more at birth is four weeks, and equipment and nurses should be provided on this basis (allowing extra time for sterilization of equipment between cases).

Percentage Born in Hospital and at Home. The incidence of premature births is lower in home deliveries (approximately 4%) than in hospital deliveries. The incidence in hospital increases with the number of abnormal cases.

Generally speaking, if 50% of all births occur in hospital, approximately 60% of the premature live births occur in hospital and 40% at home.

Hospital Care

The provision needed for premature infants in maternity hospitals will vary with the size and type of hospital. Hospitals may be divided into three types: large, medium, and small.

Large Hospitals. These should have a special unit for the smaller babies born in the hospital (under 5 lb. at birth). One hospital in each area should have extra cots in this unit for (*a*) very small or sick premature infants from smaller hospitals, and (*b*) premature infants admitted from home.

Medium-Sized Hospitals. These should each have a small nursery set aside for premature babies, with a specially trained nurse available at all times (day and night). In special circumstances (such as temporary lack of suitable staff) the smaller babies might have to be transferred to the main unit in the region.

Small Hospitals (including Private Nursing Homes). Hospitals and nursing homes with less than 600 deliveries a year have insufficient premature babies and insufficient staff to justify a separate nursery and nursing staff for premature babies, but whenever possible one nurse with experience in the care of

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the premature baby should be on the staff, however small the hospital. In small hospitals babies weighing over 4 lb. at birth may be nursed in the ordinary newborn nurseries (or in single wards with their mothers, to reduce the risk of infection) but smaller babies should be transferred as soon as possible to the main unit in the region.

Size of Premature Baby Unit. The large and medium sized hospitals accommodating only their own premature babies require one premature cot for every ten lying-in beds.

The main premature unit for the area requires in addition (*a*) for admitting cases from the home, one and a half to two cots per 1,000 domiciliary births in the area (one and a half if housing is good, two if housing is poor); (*b*) for admitting infants under 4 lb. from the small hospitals, two cots per 1,000 annual deliveries in these hospitals.

The small hospitals which keep only their larger premature infants require one premature cot to every 12 lying-in beds.

Medical Staff. Large units should have regular visits from a consultant paediatrician. This consultant should be responsible for the general plan of care and be available at all times for consultation. He or she should be assisted by other members of the paediatric staff (or junior obstetric staff) who should visit the unit daily, examine each infant on admission and before discharge, and answer emergency calls to the unit and attend the labour ward when a premature baby is being delivered.

Small units often lack expert paediatric advice and arrangements should be made to ensure the services of a consultant paediatrician, whenever one is required.

Nursing Staff. With a high proportion of very small infants the ideal ratio of nurses to infants is three nurses to four infants, but a good nursing technique can be maintained with a ratio of two nurses to three infants.

The ratio of nurses specially trained in the care of the premature baby to nurses in training (pupil midwives, postgraduate midwives, health visitors, etc.) must be kept as high as possible; ideally one to one. At least one nurse with special training must be on duty at all times (day and night) to supervise the nursing.

Accommodation. A premature baby unit is usually part of a maternity hospital, and this arrangement allows easy access to the mothers and encourages a more normal mother-baby relationship.

Elaborate new buildings are not necessary. Simple conversion of existing buildings often gives very satisfactory results.

In medium sized hospitals at least one room should be set aside for premature infants. The maximum number of cots in one room should be four and if more than this number are required, two rooms should be provided, one warm (70-75° F. and humidified) and one cool (60-65° F.); a floor space of 50 sq. ft. per cot should be allowed.

Large hospitals should set up a special premature baby unit. Ideally such a unit should include: (1) *Warm humidified rooms* for 50% of the required number of cots (maximum number of cots per room = 4). If incubators are used for the smallest infants, the number of cots required in warm humid rooms will be reduced by the number of incubators available.

(2) *Cool rooms* for the remainder of cots (maximum number of cots per room = 4).

(3) *Suspect room.* One extra cot is required for every five cots in unit (maximum number of cots per room = 2).

(4) *Single rooms for mothers.* Number required = one mother's room to every three cots.

(5) *Day room for mothers.*

(6) *Bathrooms and W.Cs. for mothers* (one of each for every six mothers).

(7) *Demonstration room.* In this room mothers who are living at home, can (*a*) breast-feed their infants, (*b*) be shown how to bath and care for their infants before taking them home. (In a large unit more than one room will be required.)

(8) *Milk kitchen.* This room should be divided into two sections: one for the reception and sterilization of used bottles and teats, and one for the preparation and storage of feeds.

(9) *Ward kitchen.*

(10) *Sluice room.*

(11) *Sterilizing room.*

(12) *Linen room.*

(13) *Duty room for nursing staff.*

Elaborate air conditioning is not necessary as long as the heating is adequate and some simple method of humidification is available. A supply of oxygen is essential, as also are wash basins.

Incubators are useful for babies under 3 lb. at birth because they save nursing time, but they are expensive, and British incubators are still in the experimental stage. It should be recognized that there are two main types of baby incubators: (1) the type which opens up and should only be used in a room heated to the temperature of the incubator; and (2) the closed type which is supplied with 'sleeves' through which the infant is handled, so that this latter type can be used in a cool room. Rooms used for incubators need not be humidified.

It is probably unwise to put very small infants into separate rooms because the danger of death from unnoticed regurgitation and inhalation is

greater than the danger of death from infection. When the baby has developed a cough reflex and the danger of suffocation is no longer serious then isolation becomes safer. With good barrier nursing, good cot spacing, the wearing of adequate masks, and the prevention of infection by dust, isolation is not necessary except in cases of infants with respiratory, intestinal, and skin infections. Such infants should be placed in the suspect room.

Domiciliary Care

Approximately 4% of all live births occurring at home are premature. Approximately 25% of these will require removal to hospital on account of low birth weight (under 4 lb.) or illness. If the housing conditions are bad 50% will benefit from hospital care.

In an ideal service the midwife who delivers a premature baby should be relieved of all other duties so that she can give special care to the baby and his mother. In such a service all midwives should have had a special training in the care of the premature baby. In practice this special training may not always be possible, and in addition, all midwives are not interested in this work. The most practical method is to have a team of specially interested and trained midwives working in association with their colleagues, available to take over the special care of premature infants born at home. The chief function of these nurses is to educate the family and help them care for their own infant.

Domiciliary care must be augmented by: (1) facilities for admission to hospital of sick infants, of infants of low birth weight, and of infants with poor home conditions; (2) medical care by the general practitioners; (3) facilities for advice from a consultant paediatrician (a rota of paediatricians available for the premature baby home care service might be circulated to all general practitioners by the medical officer of health. In the few areas where no consultant paediatrician is available suitable members of the public health staff, maternity and child welfare medical staff, might attend special courses in the care of the premature baby and be available to give advice to general practitioners); (4) adequate equipment for home care; (5) domestic help, if required; (6) transport facilities for staff and special ambulances for infants requiring removal to hospital.

Transport

Special ambulances should be available for moving infants from one hospital to another and from home to hospital. A nurse, some form of heated carrier, and facilities for the administration of oxygen are required.

Follow-up Care

Arrangements should be made for the follow-up of all premature babies and the assessment of their physical and mental status at various ages. The health visitor should take over the care of the infant when he is discharged from hospital or when special home care ceases. Full cooperation between the hospital or the midwife and the health visitor is essential.

Infants treated in hospital may be followed up by the hospital concerned but the local authority should make arrangements for the follow-up of babies treated at home, and for babies treated in hospital for whom no such arrangements have been made by the hospital.

Integration with Other Health Services

The care of the premature baby must be integrated with other health services such as the Maternity and Child Welfare Services, supply of breast milk (breast milk bank), Home Help Service.

Educational Programmes

Personnel. Each local authority should make arrangements for the training of its midwives and health visitors in the care of the premature baby.

Certain premature baby hospital units should provide courses of instruction for doctors, midwives and health visitors in hospital and domiciliary care, the latter by arrangement with the local authority.

Parents. Teaching the mother how to look after her infant should be begun in the hospital or by the premature baby nurse in the home, and should be continued in the home by the health visitor.

Research

There is need for research into the causes and prevention of prematurity and into the value of various methods of treatment.

Appraisal of Results

Regular appraisal of results is of great importance and accurate statistics are required. It is most important that the birth weight should be recorded on *all* notifications of birth (not only on those of babies with a birth weight of 5½ lb. or less, as recommended in the Ministry of Health Circular 20/44). Further, the birth weight of all stillborn infants and of infants dying during the neonatal period should be recorded; indeed it would be of value if the death certificate for all infant deaths recorded the birth weight.